

Public Assessment Report
Decentralised Procedure

Bicalutamide 50mg Film-coated Tablets

PL 20075/0074

UK/H/1154/001/DC

Accord Healthcare Limited

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Accord Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Bicalutamide 50mg Film-coated Tablets (PL 20075/0074).

Bicalutamide belongs to a group of medicines known as the non-steroidal antiandrogens and is used for the treatment of advanced prostate cancer. It is taken together with a drug known as luteinising hormone-releasing hormone analogue or with accompanying surgical removal of the testicles.

The active substance, bicalutamide, blocks the undesired effect of the male sex hormones (androgens) and inhibits cell growth in the prostate in this way.

The data submitted in support of the application for Bicalutamide 50mg Film-coated Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Bicalutamide 50mg Film-coated Tablets
Name of the active substance (INN)	Bicalutamide
Pharmacotherapeutic classification (ATC code)	L02BB03 Non-steroidal anti-androgens
Pharmaceutical form and strength	Film-coated tablet 50 mg
Reference numbers for the Decentralised Procedure	UK/H/1154/001/DC
Reference Member State	UK
Member States concerned	Belgium, Germany, Estonia, Spain, Ireland, Italy, Latvia, Malta, The Netherlands, Portugal, Slovenia and Slovakia
Date of start of the procedure	9 July 2007
End date of decentralised procedure	29 September 2008
Marketing Authorisation Number	PL 20075/0074
Name and address of the authorisation holder	Accord Healthcare Limited Sage House, 319 Pinner Road, North Harrow Middlesex, HA1 4HF, UK

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 50 mg Bicalutamide.

Excipients:

Each tablet contains 56mg of Lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off white, round biconvex, film-coated tablet debossed 'B 50' on one side and plain on other 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 Tablets 50mg should be started at least 3 days before commencing treatment with an LHRH analogue, or at the same time as surgical castration.

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

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

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

Hypersensitivity to bicalutamide or to any of the excipients:

Use in females, children and adolescents is contraindicated.
Co-administration of terfenadine, astemizole or cisapride with Bicalutamide is contra-indicated.

4.4 Special warnings and precautions for use

As there is no experience with the use of bicalutamide in patients with severe renal impairment (creatinine clearance < 30/min), bicalutamide should only be used with caution in these patients.

Bicalutamide is extensively metabolized 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), as such caution should be exercised when co-administered with drugs metabolised predominantly by CYP 3A4, see Sections 4.3 and 4.5.

Lactose: This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 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 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 Tablets 50mg are contra-indicated in females and must not be given to pregnant women or breast-feeding mothers.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, it should be noted that occasionally dizziness or somnolence may occur (see section 4.8). Any affected patients should exercise caution.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$).

Table 1 Frequency of Adverse Reactions

System organ class	Frequency	Event
Cardiac disorders	Very rare ($< 1/10,000$)	Angina, heart failure, conduction defects including PR and QT interval prolongations, arrhythmias and non-specific ECG changes.
Blood and lymphatic system disorders	Common ($\geq 1/100$, $< 1/10$)	Anaemia
	Very rare ($< 1/10,000$)	Thrombocytopenia
Nervous system disorders	Common ($\geq 1/100$, $< 1/10$)	Dizziness, insomnia.
	Uncommon ($\geq 1/1,000$, $< 1/100$)	Somnolence
Respiratory, thoracic and mediastinal disorders	Uncommon ($\geq 1/1,000$, $< 1/100$)	Interstitial lung disease, dyspnoea
Gastrointestinal disorders	Common ($\geq 1/100$, $< 1/10$)	Diarrhoea, nausea, constipation
	Uncommon ($\geq 1/1,000$, $< 1/100$)	Dry mouth, dyspepsia, flatulence.

	Rare ($\geq 1/10,000$, $< 1/1,000$)	Vomiting
Renal and urinary disorders	Uncommon ($\geq 1/1,000$, $< 1/100$)	Nocturia
Skin and subcutaneous tissue disorders	Common ($\geq 1/100$, $< 1/10$)	Rash, sweating, hirsutism
	Uncommon ($\geq 1/1,000$, $< 1/100$)	Alopecia
	Rare ($\geq 1/10,000$, $< 1/1,000$)	Dry skin
Metabolism and nutrition disorders	Common ($\geq 1/100$, $< 1/10$)	Diabetes mellitus, weight gain.
	Uncommon ($\geq 1/1,000$, $< 1/100$)	Anorexia, hyperglycaemia, Weight loss.

System organ class	Frequency	Event
General disorders and administration site condition	Very common ($\geq 1/10$)	Hot flushes ¹
	Common ($\geq 1/100$, $< 1/10$)	Asthenia, pruritus, oedema, general pain, pelvic pain, chills
	Uncommon ($\geq 1/1,000$, $< 1/100$)	Abdominal pain, chest pain, headache, pain in the back, neck pain.
Immune system disorders	Uncommon ($\geq 1/1,000$, $< 1/100$)	Hypersensitivity reactions, including angioneurotic oedema and urticaria
Hepatobiliary disorders	Common ($\geq 1/100$, $< 1/10$)	Hepatic changes (elevated levels of transaminases, cholestasis and jaundice, <u>bilirubinaemia</u>) ² , <u>hepatomegaly</u> .
	Rare ($\geq 1/10,000$, $< 1/1,000$)	Hepatic failure ³
Reproductive system and breast disorders	Very common ($\geq 1/10$)	Breast tenderness ¹ , gynaecomastia ¹

		Decreased libido, erectile dysfunction, impotence
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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)
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).

4.9 Overdose

No case of overdose has been reported. Since bicalutamide belongs to the anilide compounds there is a theoretical risk of the development of methaemoglobinaemia. Methaemoglobinaemia has been observed in animals after an overdose. Accordingly, a patient with an acute intoxication can be cyanotic. There is no specific antidote; treatment should be symptomatic. Dialysis is unlikely to 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: Hormone antagonists and related agent, non-steroidal antiandrogens, ATC code: LO2BB03.

Bicalutamide is 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 tumors results from this inhibition. Clinically, discontinuation of Bicalutamide can result in antiandrogen withdrawal syndrome in a subset of patients.

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

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 Tablets 50mg, 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 Tablets. 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 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 the 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. These comprise involution of androgen-dependent tissues; thyroid follicular adenomas, 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 have no relevance to the treatment of patients with advanced prostate cancer.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Lactose monohydrate

Sodium starch glycolate

Povidone K-30

Magnesium stearate

Coating:

Hypromellose E 5

Macrogol 400

Titanium dioxide E171

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Tablets are packed in PVC-PVdC/ aluminium blisters
Packs of 28 tablets.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA 1 4 HF-UK

8 MARKETING AUTHORISATION NUMBER

PL 20075/0074

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/10/2008

10 DATE OF REVISION OF THE TEXT

24/10/2008

Module 3

Product Information Leaflet



PACKAGE LEAFLET:
INFORMATION FOR THE USER

BICALUTAMIDE 50mg 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 Tablets is and what it is used for
2. Before you take Bicalutamide Tablets
3. How to take Bicalutamide Tablets
4. Possible side effects
5. How to store Bicalutamide Tablets
6. Further information

1. WHAT BICALUTAMIDE TABLETS IS AND WHAT IT IS USED FOR

Pharmacotherapeutic group: Hormone antagonists and related agents, anti-androgens.

Bicalutamide is used for the treatment of advanced prostatic carcinoma. It is taken together with a drug known as a luteinising hormone-releasing hormone (LHRH) analogue - an additional hormone treatment - or with accompanying surgical removal of the testicles.

Bicalutamide is one of a group of medicines known as the non-steroidal antiandrogens. The active substance bicalutamide blocks the undesired effect of the male sex hormones (androgens) and inhibits cell growth in the prostate in this way.

2. BEFORE YOU TAKE BICALUTAMIDE TABLETS

Do not take Bicalutamide Tablets if

- If you are allergic (hypersensitive) to bicalutamide or any of the other ingredients of the Bicalutamide Tablets.
- If you are a woman, adolescent or child
- If you are taking of terfenadine or astemizole (for hay fever or allergy) or cisapride (for stomach disorders), with Bicalutamide Tablets 50mg.

Bicalutamide tablets must not be taken by woman or children.

Take special care with Bicalutamide Tablets

- **If your liver functioning is moderately or severely impaired.** The drug should then only be taken after your doctor has carefully considered possible benefits and risks. If this is the case, your doctor will regularly performs tests of liver function (bilirubin, transaminases, alkaline phosphatase). If severe disturbances to liver function develop, treatment with bicalutamide should be discontinued.
- **If your renal functions is severely impaired.** The drug should then only be taken after your doctor has carefully considered possible benefits and risks.

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.

Bicalutamide may not be used together with any of the following medicines:

Terfenadine or astemizole (for hay fever or allergy), cisapride (for stomach disorders)

If you take Bicalutamide together with one of the following medicines, the effect of Bicalutamide as well as the other medicine may be influenced. Please speak to your doctor before taking any of these medicines together with Bicalutamide:

- Warfarin or any similar medicine to prevent blood clots.
- Ciclosporin (used to suppress the immune system to prevent and treat rejection of transplanted organ or bone marrow)
- Cimetidine (to treat stomach ulcers)
- Ketoconazole (used to treat fungal infections of the skin and nails)
- Ca-channel-blockers (to treat high blood pressure)

Taking Bicalutamide Tablets with food and drink:

Taking food and drink has no influence on your treatment with Bicalutamide Tablets.

Pregnancy and breast-feeding:

Bicalutamide Tablets is contra-indicated in females and must not be given to pregnant women or breast-feeding mothers. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:

Your medicine is unlikely to adversely affect the ability to drive a vehicle or to operate machinery. However, some people may occasionally feel dizzy or drowsy after taking Bicalutamide Tablets. If this happens to you, you should exercise caution when carrying out such tasks.

Important information about some of the ingredients of Bicalutamide Tablets

Bicalutamide Tablets contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE BICALUTAMIDE TABLETS

Always take Bicalutamide Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dosage of Bicalutamide tablets is one tablet daily. Swallow the tablet whole with a drink of water. Try to take your tablet at the same time each day.

If you take more Bicalutamide Tablets than you should

If you take more than prescribed dose, contact your doctor. In the case of an overdose, contact the nearest hospital immediately. If possible, take your tablets or the box with you to show the doctor what you have taken.

If you forget to take Bicalutamide Tablets

If you forget to take your medicine, take your dose when you remember and then take your next dose at the usual time. Do not take a double dose to make up for a forgotten tablet.

If you stop using Bicalutamide Tablets

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.

4. POSSIBLE SIDE EFFECTS

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The frequencies of adverse events are ranked according to the following: :

Very common: more than 1 of 10 patients treated, Common: 1 to 10 out of 100 patients treated, Uncommon: 1 to 10 out of 1,000 patients treated, Rare: 1 to 10 out of 10,000 patients treated, Very rare: less than 1 of 10,000 patients treated

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

There are usually few side effects when Bicalutamide Tablet is taken in the way your doctor or pharmacist has described.

Contact your doctor or seek medical help immediately if you experience any of the following serious side effects:

- Serious breathlessness, or sudden worsening of breathlessness, possibly with a cough or fever. Some patients taking Bicalutamide Tablets 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 Tablets are uncommon.
- Yellowing of the skin or whites of the eyes caused by liver problems (including liver failure). This side effect is rare.

Very common (more than 1 of 10 patients treated)

- Breast tenderness
- Decreased libido
- Impotence
- Gynaecomastia
- Erectile dysfunction
- Hot flushes

Common (1 to 10 out of 100 patients treated)

- Diarrhoea
- Constipation
- Nausea
- Asthenia
- Pruritus
- Oedema

- General pain
- Pelvic pain
- Chills
- Anaemia
- Diabetes mellitus
- Weight gain
- Dizziness
- Insomnia
- Rash
- Sweating
- Hirsutism
- Hepatic changes (elevated levels of transaminases, cholestatic jaundice, bilirubinaemia), enlarged liver)

Uncommon (1 to 10 out of 1,000 patients treated)

- Interstitial lung disease
- Dyspnoea
- Anorexia
- Hyperglycaemia
- Weight loss
- Somnolence
- Alopecia
- Nocturia
- Abdominal pain
- Chest pain
- Headache
- Pain in the back
- Neck pain
- Dry mouth
- Dyspepsia
- Hypersensitivity reactions, including angioneurotic oedema and urticaria, flatulence

Rare (1 to 10 out of 10,000 patients treated)

- Vomiting
- Hepatic failure
- Dry skin

Very rare (less than 1 of 10,000 patients treated)

- Conduction defects including PR and QT interval prolongations
- Heart failure, arrhythmias, non-specific ECG changes
- Thrombocytopenia.

Occasionally, Bicalutamide Tablets may be associated with changes in your blood which may require your doctor to do certain blood tests.

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 TABLETS

- This medicinal product does not require any special storage conditions
- Keep out of the reach and sight of children.
- Do not use Bicalutamide Tablets after the expiry date which is stated on the Carton and blister (EXP). The expiry date refers to the last day of that month e.g. mm/yyyy.
- 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 Tablets contains:

The active substance is Bicalutamide. Each film-coated tablet contains 50mg of bicalutamide.

Excipients:

Tablet core:

lactose monohydrate
sodium starch glycolate (Type A)
povidone K-30
magnesium stearate.

Film coat:

Hypromellose E5
titanium dioxide E171
Macrogol 400.

What Bicalutamide Tablets looks like and content of the pack:

Bicalutamide 50 mg film-coated Tablet is a white to off white, round biconvex, film-coated tablets debossed 'B 50' on one side and plain on other side.

Bicalutamide 50 mg film-coated Tablets are packed in blisters in pack of 28 tablets.

Marketing Authorisation Holder and Manufacturer:

Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex HA1 4HF, UK

The leaflet was last approved in October 2008

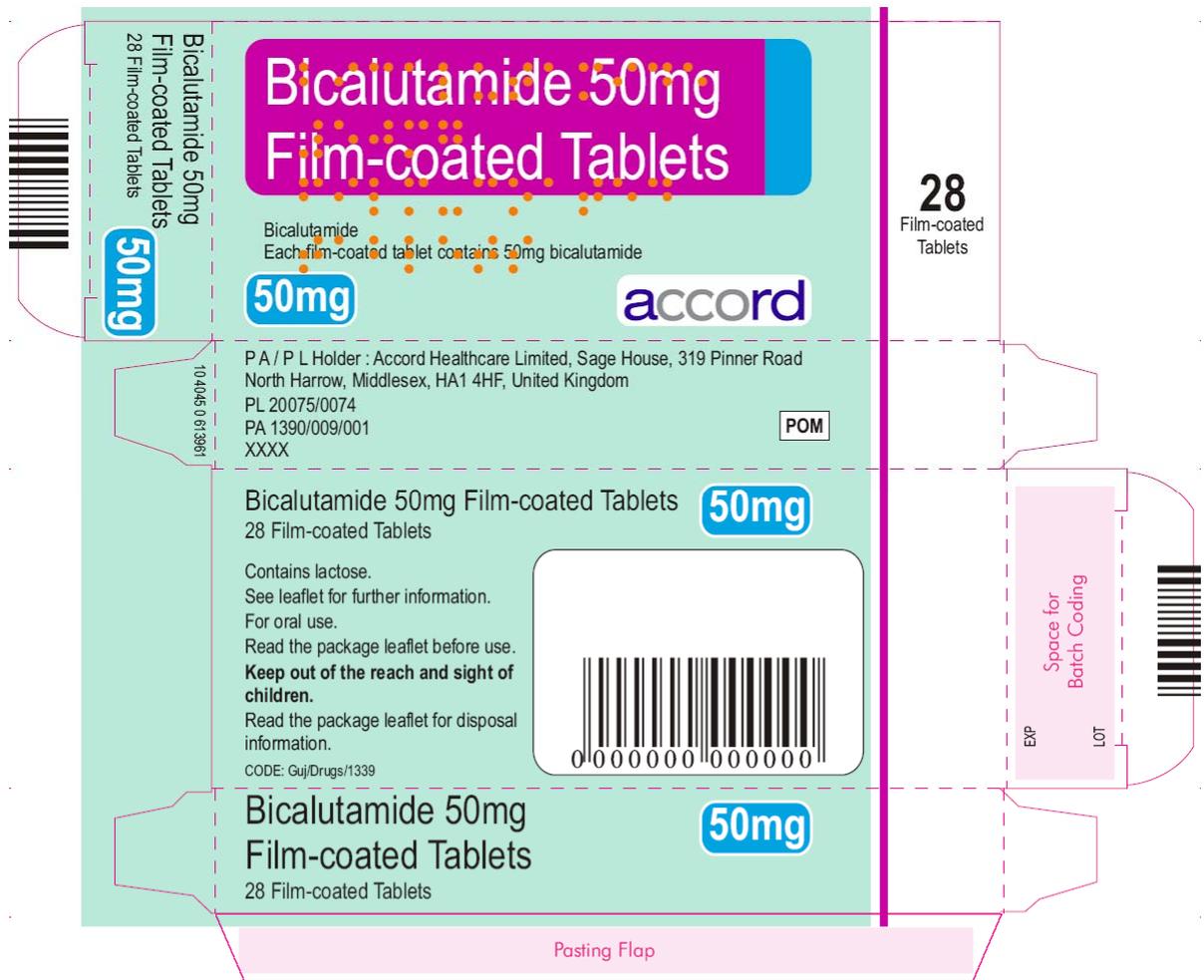
Module 4

Labelling

Blister:



Carton:



Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Bicalutamide 50mg Film-coated Tablets in the treatment of advanced prostate cancer in combination with LHRH analogues or surgical bilateral orchiectomy could be approved.

EXECUTIVE SUMMARY

PROBLEM STATEMENT

This application has been submitted under Article 10(1) of Directive 2001/83/EC, as amended. The product is claimed to be generic to a reference product that has been authorised in the EEA for over 10 years and the application is considered valid.

With the UK as the Reference Member State in this Decentralised Procedure, Accord Healthcare Limited applied for a Marketing Authorisation for Bicalutamide 50mg Film-coated Tablets in Belgium, Germany, Estonia, Spain, Ireland, Italy, Latvia, Malta, The Netherlands, Portugal, Slovenia and Slovakia.

About the product

Bicalutamide is a non-steroidal antiandrogen, devoid of other endocrine activity. It is an androgen receptor blocker that prevents the physiological effects of dihydrotestosterone and, therefore, competitively antagonizes the actions of androgens. It binds to androgen receptors without activating gene expression and, thus, inhibits the androgen stimulus. Regression of prostatic tumours results from this inhibition.

With antiandrogenic activity being almost exclusively exhibited by the R-enantiomer of bicalutamide; the S-enantiomer is essentially inactive. The compound has shown efficacy in the treatment of advanced prostate cancer.

The absolute bioavailability of bicalutamide is not known, but the drug is apparently well absorbed after an oral dose. Food does not affect bicalutamide absorption, which is dose-dependent and prolonged. The drug is highly bound to plasma proteins (>95%).

Bicalutamide undergoes stereoselective metabolism. The S isomer (inactive) is metabolized by glucuronidation. The R isomer (active) mainly undergoes oxidation to form an inactive metabolite, which is further glucuronized. The minor pathway of the R isomer is direct glucuronidation. The S isomer is rapidly cleared relative to the R isomer, with the R enantiomer accounting for approximately 99% of total steady state plasma levels. Both the parent compound and metabolites are excreted in urine and faeces.

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.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

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.

The applicant has given an undertaking that the bioequivalence study was conducted in compliance with the GLP and GCP.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

There is no Ph Eur monograph for bicalutamide, but the control tests and specification for the drug substance are adequately drawn up. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed and the proposed retest period is justified.

Drug 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 and the 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 of 24 months with no specific storage conditions for the drug product is considered acceptable.

Non-clinical aspects

The 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 has not provided any. A literature-based overview is, therefore, appropriate and there are no non-clinical issues arising from the inclusion of bicalutamide in the proposed formulation.

Clinical aspects

No new efficacy and safety data were submitted and none is required for this type of application.

To support the application, the applicant has submitted one single dose bioequivalence study.

Pharmacokinetic study

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioavailability study in healthy, adult, human male subjects under fasting conditions was conducted to compare the bioavailability and characterise the pharmacokinetic profile of the applicant's formulation compared to the reference formulation (Casodex 50 mg tablets) and to assess the bioequivalence.

Forty-six subjects aged between 18 and 55 years with a Body Mass Index (BMI) between 18.5 kg/m² and 24.9 kg/m² were included in the study. Subjects were in good health, having no significant diseases or clinically significant abnormal laboratory values during screening, medical history, physical examination, chest X-ray, 12-lead ECG recordings or laboratory evaluations, including negative HIV, Hepatitis B and Hepatitis C tests as well as negative screening of ethyl alcohol and drugs of abuse in urine.

Subjects were instructed to abstain from consuming any xanthine-containing food or beverages (like chocolates, tea, coffee or cola drinks), tobacco, tobacco-containing products or cigarettes for 24 hours prior to dosing in each period and throughout their stay in the clinical facility. Subjects were required to refrain from any medication for 7 days prior to the study and no prescription drugs were allowed during the 14 days prior to the study. Enzyme activity modifying drugs were not allowed 28 days prior the study. During the study session, no medication was allowed.

Seven subjects were excluded from the efficacy analysis. Five subjects were withdrawn; two of their accord and three for not satisfying the protocol requirement. Their plasma samples were not analysed. Two subjects were withdrawn from the trial on medical grounds, their plasma samples were analysed, but their data were excluded from the pharmacokinetic and statistical analyses, as per the requirement of the protocol. In all, plasma samples of forty-one subjects (thirty-nine subjects who completed the trial successfully and two subjects who were withdrawn from the trial on medical grounds) were analysed.

One tablet was administered orally to each subject with 240 mL water while in sitting posture, after an overnight fast of at least 10 hours. This procedure was followed by a mouth check. The subjects were not allowed to lie down for the first three hours after dosing.

Serial blood sampling before dosing and up to 504 hours post-dose administration was carried out in each period. Samples were collected on an ambulatory basis at and after 72 hours. A total of twenty-two blood samples (3 mL each) were collected for each subject in each period. The venous blood samples were withdrawn at pre-dose and at 2, 4, 6, 8, 10, 12, 16, 20, 24, 26, 28, 30, 32, 34, 36, 48, 72, 120, 168, 336 and 504 hours following administration in each period. A washout period of 59 days was maintained between the two successive dosing days.

The criteria for evaluation were based on the pharmacokinetic parameters, C_{max} , AUC_{0-t} and $AUC_{0-\infty}$, of the bicalutamide data. The two one-sided 90% parametric confidence intervals were constructed for ln-transformed pharmacokinetic parameters: C_{max} , AUC_{0-t} and $AUC_{0-\infty}$, for bicalutamide.

Results:

Table-A: Descriptive Statistics of Formulation Means for Bicalutamide (n=39)

Parameters (unit)	Mean \pm SD	
	Reference Product A	Reference product B
T _{max} (h)	28	30
C _{max} (ng/mL)	1008.2 \pm 152.8	877.5 \pm 163.7
AUC _{0-t} (ng.h/mL)	197680.6 \pm 47810.7	176823.1 \pm 39033.8
AUC _{0-∞} (ng.h/mL)	222852.3 \pm 49874.0	194364.0 \pm 43634.6

Table-B: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Bicalutamide (n=39) (ln-transformed)

Parameters (unit)	Geometric Least	Squares	Mean	90% Confidence
	Test Product-B	Test Product-A	Ratio (B / A)%	Interval (Parametric)
C _{max} (ng / mL)	874.2	997.0	87.7	83.4 - 92.2
AUC _{0-t} (ng.h / mL)	172379.0	191428.4	90.0	84.5 - 96.1
AUC _{0-∞} (ng.h / mL)**	189687.9	215879.7	87.9	82.4 - 93.7

Note **34

Assessor's Conclusion:

- The applicant has provided a single bioequivalence study using the test and reference products.
- The number of subjects in the study is adequate and the conduct of the study, as described in the report, is consistent with the principle of GCP.
- The plasma sampling scheme was adequate.
- Data were reported for 39 subjects.
- The design chosen agrees with national and EMEA guidelines on bioavailability/bioequivalence studies.

Therefore, bioequivalence between the test and reference products was demonstrated.

Pharmacovigilance system

Based on the available information, it is concluded that there is no important new safety information. The proposed wording of SPC reflects up to date knowledge and recommendations.

Risk Management Plan

The need for a Risk Management Plan (RMP) for bicalutamide has been reviewed. Accord Healthcare has compiled the proposed SPC on the basis of the innovator product, Casodex (AstraZeneca) and a review of the current literature, which was conducted specifically to identify new/emerging safety issues and any recommendations made by regulatory authorities in relation to issues or Adverse Drug Reactions (ADRs) that are not currently listed on the SPC of the innovator brand. However, no concerns were identified and a risk management plan is, therefore, not included with this application.

BENEFIT RISK ASSESSMENT

The application contains an adequate review of the published clinical data and bioequivalence between the test and reference products has been shown.

The benefit-risk ratio is considered positive. Granting of a Marketing Authorisation for Bicalutamide 50mg Film-coated Tablets is recommended.

Overall conclusion

QUALITY

The important quality characteristics of Bicalutamide 50mg Film-coated Tablets are well defined and controlled. The specification 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 preclinical data is needed for this application.

No new or unexpected safety concerns arise from this application.

EFFICACY

Previous clinical studies have demonstrated the efficacy of bicalutamide in the treatment of prostate cancer.

The product literature is satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.