Public Assessment Report

Decentralised Procedure

Bicalutamide 50mg and 150mg Film-coated Tablets

Bicalutamide

UK/H/1245/01-02/DC

UK licence no: PL 10622/0330-1

Applicant: PLIVA Pharma Ltd

LAY SUMMARY

The MHRA granted Pliva Pharma Limited Marketing Authorisations (licences) for the medicinal products Bicalutamide 50mg (PL 10622/0330) and 150mg Film coated Tablets (PL 10622/0331) on 2nd October 2008. These are prescription-only medicines (POM) that are used for the treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration.

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.

It is also used for the treatment of advanced prostate 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.

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

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Module 1

Product Name	Bicalutamide 50mg and 150mg film-coated tablets
Type of Application	Generic, Article 10.1
Active Substance	Bicalutamide
Form	Film-Coated Tablets
Strength	50mg and 150mg Film-Coated Tablets
MA Holder	PLIVA Pharma Limited, Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB – United Kingdom
RMS	UK
CMS	50mg: CZ, DE, EE, HU, IE, LT, LV, PL, SI, and SK 150mg: CZ, DE, HU, IE, PL, SI, SK
Procedure Number	UK/H/1245/01-02/DC:
Timetable	Day 210: 1st September 2008

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 of bicalutamide

Excipients:
Each tablet contains 1.04mg of lactose (as lactose monohydrate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

White or almost white round, biconvex, film-coated tablet, imprinted with 'BC' on one side and '50' on the other side.

4 CLINICAL PARTICULARS

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

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

Route: oral
The tablets should be swallowed whole with liquid.

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

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

Renal impairment: no dose 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 < 30 ml/min) (see section 4.4)

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

4.3 Contraindications
Hypersensitivity to bicalutamide or any of the excipients.

Bicalutamide is contraindicated in women 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 metabolised in the liver. Research results suggest that bicalutamide's elimination may be slower in patients 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.

Severe hepatic damages have been rarely observed with bicalutamide (see section 4.8). Bicalutamide therapy should be discontinued if changes are severe.

Periodic liver function testing is warranted in order to find out about possible hepatic changes. The majority of changes are expected to occur within the first 6 months of bicalutamide therapy.

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

Periodical monitoring of cardiac function is advisable in patients with heart disease.

Initiation of treatment should be under the direct supervision of a specialist and subsequently patients should be kept under regular surveillance.

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

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacodynamic or pharmacokinetic interactions have been demonstrated between bicalutamide and LHRH analogues.

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

Although *in vitro* studies have indicated the possibility of bicalutamide inhibiting cytochrome 3A4, a number of clinical studies show that the scale of this inhibition for most drugs metabolised by cytochrome P450 is probably not clinically significant.

Nonetheless, for drugs with a narrow therapeutic index metabolised in the liver, the CYP 3A4 inhibition caused by bicalutamide could be of relevance. As such, concomitant use of terfenadine, astemizole and cisapride is contraindicated. 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 administering bicalutamide to patients taking medicinal products that inhibit the oxidation process in the liver e.g. cimetidine and ketoconazole. 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 prothrombin time is closely monitored if bicalutamide is started in patients who are already receiving coumarin anticoagulants.

4.6 Pregnancy and lactation

Not applicable, since this medicinal product is not used in women.

Fertility

Reversible impairment of male fertility has been observed in animal studies (see section 5.3). A period of subfertility or infertility should be assumed in man.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, it should be noted that occasionally dizziness and somnolence may occur (see section 4.8). Any affected patients should exercise caution.

4.8 Undesirable effects

Adverse events observed with bicalutamide are classified in body systems and listed below as:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10000 to <1/1000)
Very rare (<1/10000), not known (cannot be estimated from the available data).

Immune system disorders
Uncommon: Hypersensitivity reactions, including angio-oedema and urticaria

Psychiatric disorders
Uncommon: Depression

Respiratory, thoracic and mediastinal disorders
Uncommon: Interstitial lung disease

Gastrointestinal disorders
Common: Diarrhoea, nausea
Rare: Vomiting

Hepatobiliary disorders
Common: Hepatic changes (elevated levels of transaminases, cholestasis and jaundice)[1]
Very rare: Hepatic failure[2]

Skin and subcutaneous tissue disorders
Common: Pruritus
Rare: Dry skin

Renal and urinary disorders
Uncommon: Haematuria

Reproductive system and breast disorders
Very common: Breast tenderness[3], gynaecomastia[3]

General disorders and administration site conditions
Very common: Hot flushes[3]
Common: Asthenia

[1] Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4).
[2]Hepatic failure has occurred very rarely in patients treated with bicalutamide, but a casual relationship has not been established with certainty. Periodic liver function testing should be considered (see also section 4.4).
[3]May be reduced by concomitant castration.

In addition, the following adverse experiences were reported in clinical trials during treatment with bicalutamide with/without a LHRH analogue:

Blood and lymphatic system disorders
Common: Anaemia
Very rare: Thrombocytopenia

Metabolism and nutrition disorders
Common: Diabetes mellitus, weight gain
Uncommon: Anorexia, hyperglycaemia, weight loss

Nervous system disorders
Common: Dizziness, insomnia
Uncommon: Somnolence

Cardiac disorders
Very rare: Heart failure, angina, conduction defects including PR and QT interval prolongations, arrhythmias and non-specific ECG changes

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea

Gastrointestinal disorders
Common: Constipation

Uncommon: Dry mouth, dyspepsia, flatulence

Skin and subcutaneous tissue disorders
Common: Rash, sweating, hirsutism
Uncommon: Alopecia

Renal and urinary disorders
Uncommon: Nocturia

Reproductive system and breast disorders
Very common: Decreased libido, erectile dysfunction, impotence

General disorders and administration site conditions
Common: Oedema, general pain, pelvic pain, chills
Uncommon: Abdominal pain, chest pain, headache, pain in the back, neck pain

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: Anti-androgens, ATC Code: L02B 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 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.

Following a long-term administration of bicalutamide, the peak concentration of the (R)-enantiomer in the plasma is about 10 fold, as compared to the levels measured after a single dose of 50mg bicalutamide.

A dosing scheme of 50 mg bicalutamide daily will result in a steady-state concentration of the R-enantiomer of 9 μg/ml and as a consequence of its long half-life, steady state is reached after approximately 1 month of therapy.

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

Bicalutamide is highly protein bound (racemate 96%, (R)-enantiomer >99%) and extensively metabolised (by 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.

Atrophy of seminiferous tubules is a predicted class effect with antiandrogens and has been observed for all species examined. Full reversal of testicular atrophy was 24 weeks after a 12-month repeated dose toxicity study in rats, although functional reversal was evident in reproduction studies 7 weeks after the end of an 11 week dosing period. A period of subfertility or infertility should be assumed in man.

Genotoxicity studies did not reveal any mutagenic potential of bicalutamide.

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

Tablet core:
Cellulose, Microcrystalline
Povidone
Sodium laurilsulfate
Croscarmellose sodium
Sodium starch glycolate (Type C)
Magnesium stearate

Coating:
Opadry II 31F58914 white
ContainsHypromellose E464
Lactose monohydrate
Titanium dioxide E171
Macrogol 4000
Sodium citrate dihydrate E331(c)

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

PVC//Aluminium blister
Pack sizes: 28, 30, 40, 90

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

PLIVA Pharma Limited.
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0330

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/10/2008

10 DATE OF REVISION OF THE TEXT
02/10/2008

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide 150mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150mg of bicalutamide

Excipients:
Each tablet contains 3.1mg of lactose (as lactose monohydrate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to almost white round, biconvex, film-coated tablet, imprinted with 'BC' on one side and '150' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Adult males including the elderly: one tablet (150mg) to be taken orally once a day.

Route: oral
The tablets should be swallowed whole with liquid.

Bicalutamide 150 mg should be taken continuously for at least 2 years or until disease progression.

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

Renal impairment: no dose 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 <30 ml/min) (see section 4.4).

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

4.3 Contraindications

Hypersensitivity to bicalutamide or any of the excipients

Bicalutamide is contraindicated in women 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 metabolised in the liver. Research results suggest that bicalutamide's elimination may be slower in patients with severe hepatic impairment and that this could lead to increased accumulation of bicalutamide. Therefore, bicalutamide should be used with caution in patients with moderate to severe hepatic impairment.

Severe hepatic changes have been rarely observed with bicalutamide (see section 4.8). Bicalutamide therapy should be discontinued if changes are severe.

Periodic liver function testing is warranted in order to find out about possible hepatic changes. The majority of changes are expected to occur within the first 6 months of bicalutamide therapy.

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

Periodic monitoring of cardiac function is advisable in patients with heart disease.

For patients who have an objective progression of disease together with elevated PSA, cessation of bicalutamide therapy should be considered.

Initiation of treatment should be under the direct supervision of a specialist and subsequently patients should be kept under regular surveillance.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Although *in vitro* studies have indicated the possibility of bicalutamide inhibiting cytochrome 3A4, a number of clinical studies show that the scale of this inhibition for most drugs metabolized by cytochrome P450 is probably not clinically significant.

Nonetheless, for drugs with a narrow therapeutic index metabolized in the liver, the CYP 3A4 inhibition caused by bicalutamide could be of relevance. As such, concomitant use of terfenadine, astemizole and cisapride is contraindicated.

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 administering bicalutamide to patients taking medicinal products that inhibit the oxidation process in the liver e.g. cimetidine and ketoconazole. 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 prothrombin time is closely monitored if bicalutamide is started in patients who are already receiving coumarin anticoagulants.

4.6 Pregnancy and lactation

Not applicable, since this medicinal product is not used in women.

Fertility

Reversible impairment of male fertility has been observed in animal studies (see section 5.3). A period of subfertility or infertility should be assumed in man.

4.7 Effects on ability to drive and use machines

No studies on the effects 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

Adverse events observed with bicalutamide are classified in body systems and listed below as:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10000 to <1/1000)
Very rare (<1/10000), not known (cannot be estimated from the available data).

Immune system disorders

Uncommon: Hypersensitivity reactions, including angio-oedema and urticaria

Psychiatric disorders
Uncommon: Depression

Respiratory, thoracic and mediastinal disorders
Uncommon: Interstitial lung disease

Gastrointestinal disorders
Common: Diarrhoea, nausea
Rare: Vomiting

Hepatobiliary disorders
Common: Hepatic changes (elevated levels of transaminases, cholestasis and jaundice)[1]
Very rare: Hepatic failure[2]

Skin and subcutaneous tissue disorders
Common: Pruritus
Rare: Dry skin

Renal and urinary disorders
Uncommon: Haematuria

Reproductive system and breast disorders
Very common: Breast tenderness[3], gynaecomastia[3]

General disorders and administration site conditions
Very common: Hot flushes[3]
Common: Asthenia
[1]Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4).
[2]Hepatic failure has occurred very rarely in patients treated with bicalutamide, but a casual relationship has not been established with certainty. Periodic liver function testing should be considered (see also section 4.4).
[3]May be reduced by concomitant castration.

In addition, the following adverse experiences were reported in clinical trials during treatment with /without a LHRH analogue:

Blood and lymphatic system disorders
Common: Anaemia
Very rare: Thrombocytopenia

Metabolism and nutrition disorders
Common: Diabetes mellitus, weight gain
Uncommon: Anorexia, hyperglycaemia, weight loss

Nervous system disorders
Common: Dizziness, insomnia
Uncommon: Somnolence

Cardiac disorders
Very rare: Heart failure, angina, conduction defects including PR and QT interval prolongations, arrhythmias and non- specific ECG changes

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea

Gastrointestinal disorders
Common: Constipation
Uncommon: Dry mouth, dyspepsia, flatulence

Skin and subcutaneous tissue disorders

Common: Rash, sweating, hirsutism
Uncommon: Alopecia

Renal and urinary disorders
Uncommon: Nocturia

Reproductive system and breast disorders
Very common: Decreased libido, erectile dysfunction, impotence

General disorders and administration site conditions
Common: Oedema, general pain, pelvic pain, chills
Uncommon: Abdominal pain, chest pain, headache, pain in the back, neck pain

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: Anti-androgens, ATC Code: L02B 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 can result in antiandrogen withdrawal syndrome in a subset of patients.

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

Bicalutamide 150 mg was studied as a treatment for patients with localised (T1-T2, N0 or NX, M0) or locally advanced (T3-T4, any N, M0; T1-T2, N+, M0) non-metastatic prostate cancer in a combined analysis of three placebo controlled, double-blind studies in 8113 patients, where bicalutamide was given as immediate hormonal therapy or as adjuvant to radical prostatectomy or radiotherapy, (primarily external beam radiation). At 7.4 years median follow up, 27.4% and 30.7% of all bicalutamide and placebo-treated patients, respectively, had experienced objective disease progression.

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

No overall survival difference was seen at 7.4 years median follow up with 22.9% mortality (HR= 0.99; 95% CI 0.91 to1.09). However, some trends were apparent in exploratory subgroup analyses.

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

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

Analysis population	**Events (%) in Bicalutamide patients**	**Events (%) in placebo patients**	**Hazard ratio (95% CI)**
Watchful waiting	193/335 (57.6)	222/322 (68.9)	0.60 (0.49 to 0.73)
Radiotherapy	66/161 (41.0)	86/144 (59.7)	0.56 (0.40 to 0.78)

Radical prostatectomy	179/870 (20.6)	213/849 (25.1)	0.75 (0.61 to 0.91)

Overall survival in locally advanced disease by therapy sub-group

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

For patients with localised disease receiving bicalutamide alone, there was no significant difference in progression free survival. In these patients there was also a trend toward decreased survival compared with placebo patients (HR= 1.16; 95% CI 0.99 to1.37). In view of this, the benefit-risk profile for the use of bicalutamide is not considered favourable in this group of patients.

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.

Following a long-term administration of bicalutamide the peak concentration of the (R)-enantiomer in the plasma is about 10-fold, as compared to the levels measured after a single dose of 50 mg of bicalutamide.

A dosing scheme of 150 mg bicalutamide daily will result in a steady-state concentration of the R-enantiomer of 22 µg /ml and as a consequence of its long half-life, steady state is reached after approximately 1 month of therapy.

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

Bicalutamide is highly protein bound (racemate 96%, (R)-enantiomer >99%) and extensively metabolised (by oxidation and glucuronidation). Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

In a clinical study the mean concentration of (R)-enantiomer of bicalutamide in semen of men receiving bicalutamide 150mg was 4.9 microgram/ml. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and equates to approximately 0.3 microgram/kg. This is below that required to induce changes in offspring of laboratory animals.

5.3 Preclinical safety data

Bicalutamide is a pure and potent androgen receptor antagonist in experimental animals and humans. The main secondary pharmacological action is induction of CYP450 dependent mixed function oxidases in 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.

Atrophy of seminiferous tubules is a predicted class effect with antiandrogens and has been observed for all species examined. Full reversal of testicular atrophy was 24 weeks after a 12-month repeated dose toxicity study in rats, although functional reversal was evident in reproduction studies 7 weeks after the end of an 11 week dosing period. A period of subfertility or infertility should be assumed in man.

Genotoxicity studies did not reveal any mutagenic potential of bicalutamide.

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

Tablet core:
Cellulose,Microcrystalline
Povidone
Sodium laurilsulfate
Croscarmellose sodium
Sodium starch glycolate (Type C)
Magnesium stearate

Coating:
Opadry II 31F58914 white

ContainsHypromellose E464
Lactose monohydrate
Titanium dioxide E171
Macrogol 4000
Sodium citrate dihydrate E331(c)

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

PVC//Aluminium blister
Pack sizes: 28, 30, 40, 90
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

PLIVA Pharma Limited.
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0331

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/10/2008

10 DATE OF REVISION OF THE TEXT

02/10/2008

Module 3

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 these tablets are and what they are used for**
2. **Before you take your medicine**
3. **How to take your medicine**
4. **Possible side effects**
5. **How to store your medicine**
6. **Further information**

❶ What these tablets are and what they are used for

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.

Bicalutamide 50mg Tablets are used for the treatment of advanced prostate 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.

2 Before you take your medicine

Do not take this medicine:

- If you are allergic (hypersensitive) to bicalutamide or any of the other ingredients of bicalutamide tablets (see Section 6 for other ingredients)
- If you take terfenadine (for hay fever or allergy), astemizole (for hay fever or allergy) or cisapride (for stomach disorders)
- Bicalutamide tablets should not be given to women or to children and adolescents

Take special care with these tablets

- **If your liver function 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 perform tests of liver function (bilirubin, transaminases, alkaline phosphatase). If severe disturbances to liver function develop, treatment with this medicine 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
- **If you suffer from heart disease.** If this is the case, your doctor should regularly monitor your heart function

Taking or using 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.

This medicine 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 this medicine 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 a transplanted organ or bone marrow)
- Cimetidine (to treat stomach ulcers)
- Ketoconazole (used to treat fungal infections of the skin and nails)
- Calcium-channel blockers (to treat high blood pressure)

Taking Bicalutamide 50mg Tablets with food and drink

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

Pregnancy and breast-feeding

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

Bicalutamide is contraindicated in females and must not be given to pregnant or breast-feeding mothers.

Driving and using machines

There is a possibility that these tablets could make you feel dizzy or drowsy. If you are affected in this way, you should not drive or operate machinery.

Important information about the ingredients of your tablet

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 your medicine

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

The doctor prescribes an appropriate dosage for you personally. The usual dose is one tablet once daily. Read the instruction label on the package.

Tablets are swallowed whole with some liquid. Try to take the medicinal product approximately at the same time each day.

If you take more tablets than you should

If you have taken too many tablets contact your doctor or the nearest hospital as soon as possible. Take with you the remaining tablets or the pack so the doctor can identify what you have taken. Symptoms of overdose: a bluish discolouration of the skin and mucous membranes.

If you forget to take a dose of your medicine

If you forget to take your daily dose, skip it when you remember it and wait until the next administration time. Do not take a double dose to make up for a forgotten dose.

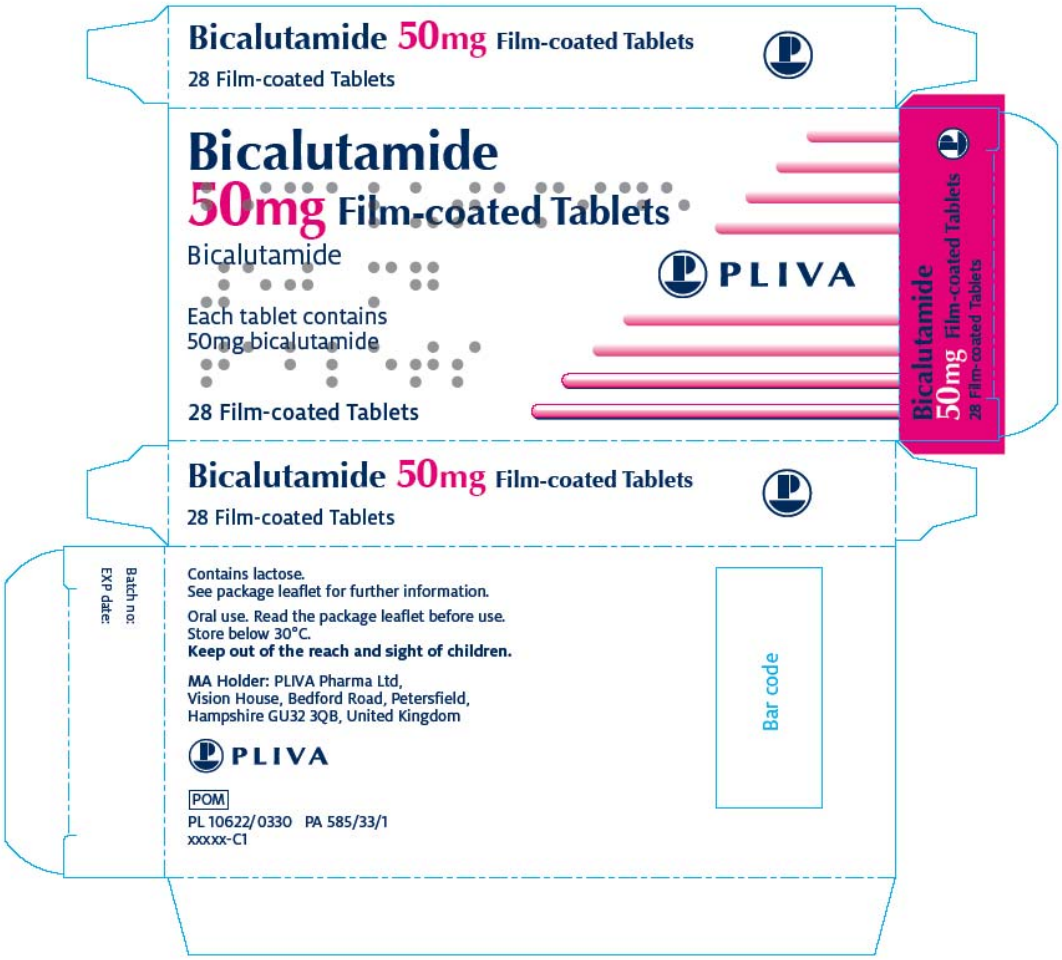
If you stop taking your medicine

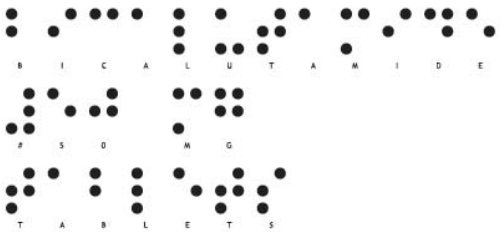
Do not stop taking this medicine even if you feel healthy unless so advised by your doctor.

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

Module 4

Labelling

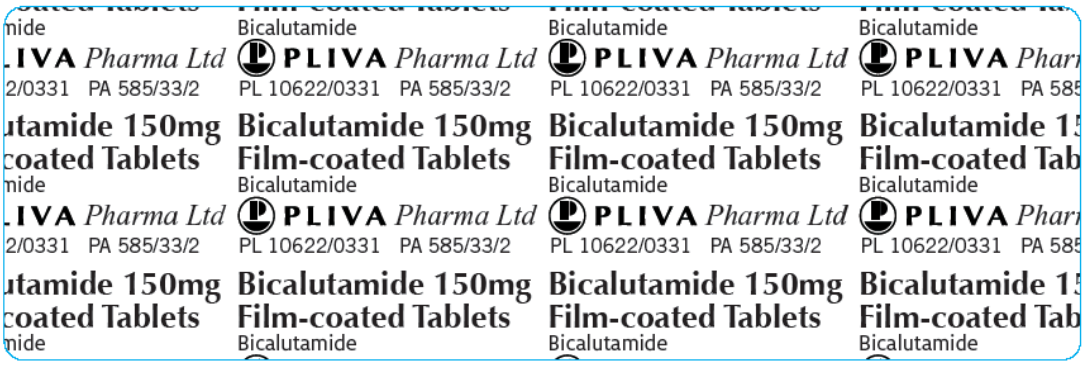

Bicalutamide 50mg Film-coated Tablets
28 Film-coated Tablets
Bicalutamide
50mg Film-coated Tablets
Bicalutamide
Each tablet contains
50mg bicalutamide
28 Film-coated Tablets
PLIVA
Bicalutamide 50mg Film-coated Tablets
28 Film-coated Tablets
Bicalutamide 50mg Film-coated Tablets
28 Film-coated Tablets
Batch no:
EXP date:
Contains lactose.
See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store below 30°C.
Keep out of the reach and sight of children.
MA Holder: PLIVA Pharma Ltd,
Vision House, Bedford Road, Petersfield,
Hampshire GU32 3QB, United Kingdom
PLIVA
POM
PL 10622/0330 PA 585/33/1
xxxxx-C1
Bar code

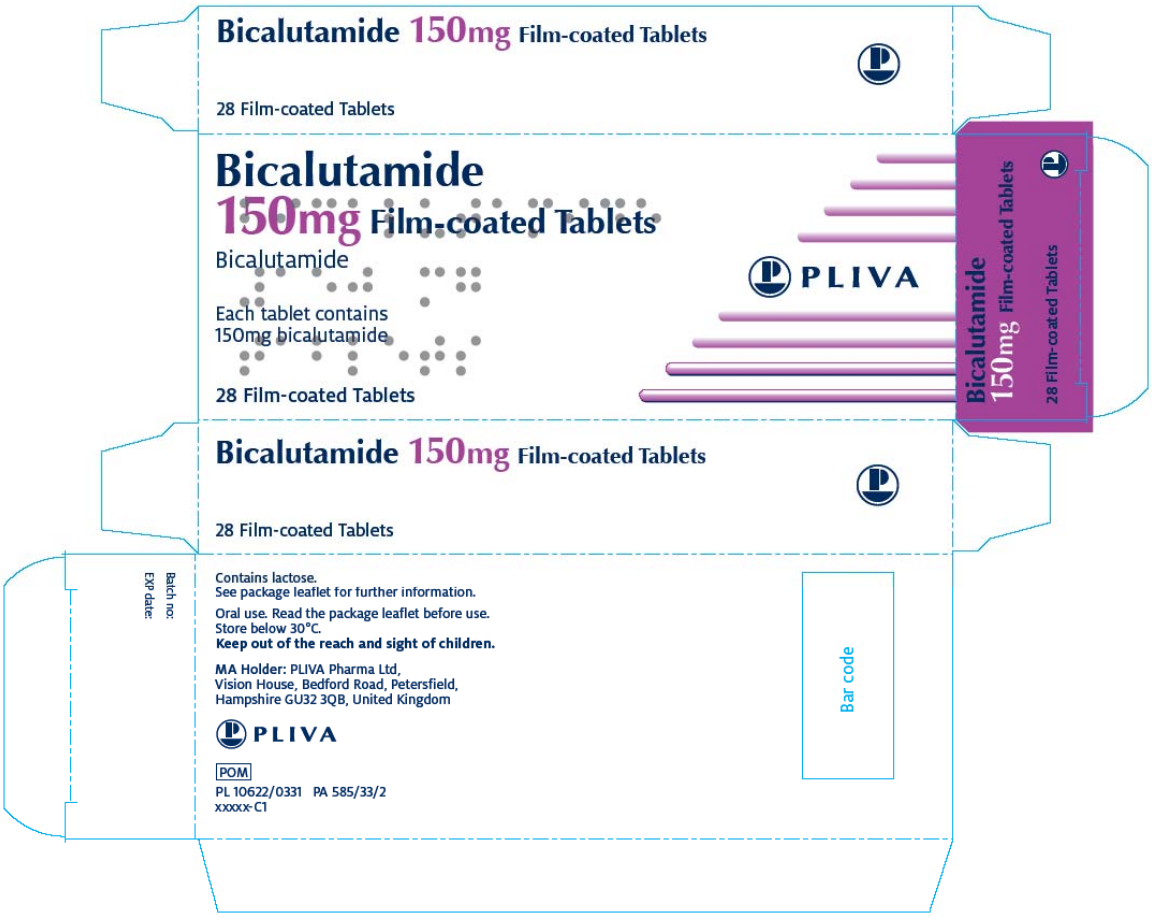

BICALUTAMIDE
50MG
TABLETS

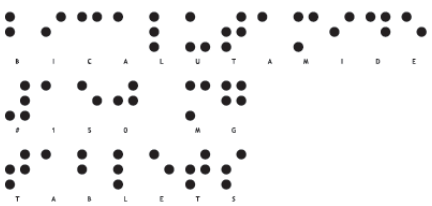

Bicalutamide
50mg Film-coated Tablets
30 Film-coated Tablets
Bicalutamide
50mg Film-coated Tablets
Bicalutamide
Each tablet contains
50mg bicalutamide
30 Film-coated Tablets
PLIVA
Bicalutamide
50mg Film-coated Tablets
30 Film-coated Tablets
Bicalutamide
50mg Film-coated Tablets
30 Film-coated Tablets
Batch no:
EXP date:
Contains lactose.
See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store below 30°C.
Keep out of the reach and sight of children.
MA Holder: PLIVA Pharma Ltd,
Vision House, Bedford Road, Petersfield,
Hampshire GU32 3QB, United Kingdom
PLIVA
POM
PL 10622/0330 PA 585/33/1
xxxxx-C1
Bar code

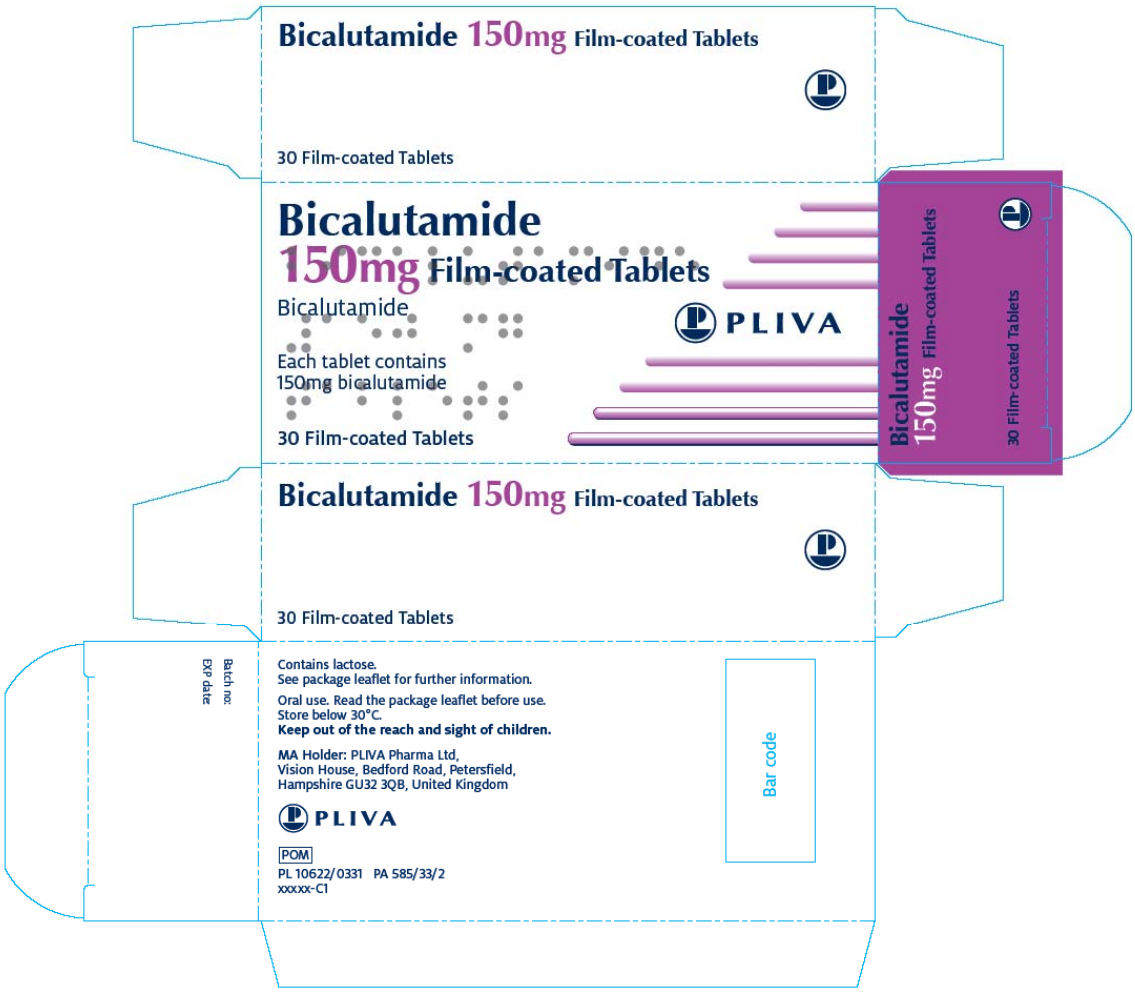

Bicalutamide
50mg Film-coated Tablets
40 Film-coated Tablets
Bicalutamide
50mg Film-coated Tablets
Bicalutamide
Each tablet contains
50mg bicalutamide
40 Film-coated Tablets
PLIVA
Bicalutamide
50mg Film-coated Tablets
40 Film-coated Tablets
Bicalutamide
50mg Film-coated Tablets
40 Film-coated Tablets
Batch no:
Exp date:
Contains lactose.
See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store below 30°C.
Keep out of the reach and sight of children.
MA Holder: PLIVA Pharma Ltd,
Vision House, Bedford Road, Petersfield,
Hampshire GU32 3QB, United Kingdom
PLIVA
POM
PL 10622/0330 PA 585/33/1
xxxxx-C1
Bar code

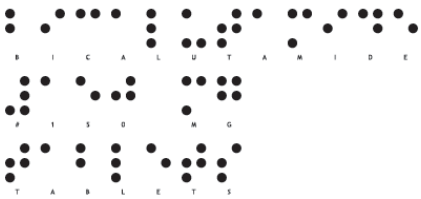

Bicalutamide
50mg Film-coated Tablets
Bicalutamide
90 Film-coated Tablets
Bicalutamide
50mg Film-coated Tablets
Bicalutamide
PLIVA
Each tablet contains
50mg bicalutamide
90 Film-coated Tablets
Bicalutamide
50mg Film-coated Tablets
90 Film-coated Tablets
Bicalutamide
50mg Film-coated Tablets
Bicalutamide
90 Film-coated Tablets
Contains lactose.
See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store below 30°C.
Keep out of the reach and sight of children.
MA Holder: PLIVA Pharma Ltd,
Vision House, Bedford Road, Petersfield,
Hampshire GU32 3QB, United Kingdom
PLIVA
POM
PL 10622/0330 PA 585/33/1
xxxxx-C1
Bar code

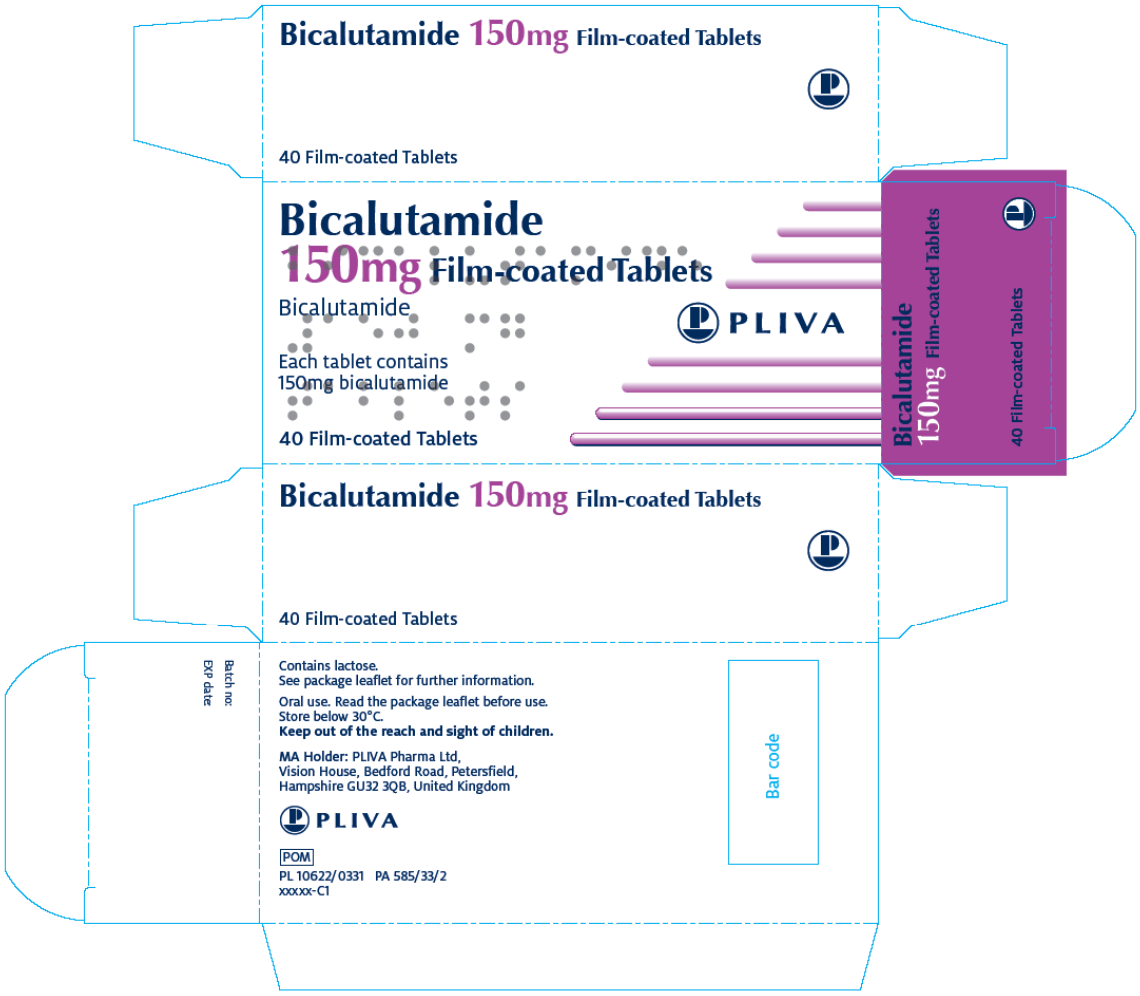

Bicalutamide
PLIVA Pharma Ltd
PL 10622/0331 PA 585/33/2
Bicalutamide 150mg
Film-coated Tablets


Bicalutamide 150mg Film-coated Tablets
28 Film-coated Tablets
Bicalutamide
150mg Film-coated Tablets
Bicalutamide
Each tablet contains
150mg bicalutamide
28 Film-coated Tablets
PLIVA
Bicalutamide 150mg Film-coated Tablets
28 Film-coated Tablets
Batch no:
EXP date:
Contains lactose.
See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store below 30°C.
Keep out of the reach and sight of children.
MA Holder: PLIVA Pharma Ltd,
Vision House, Bedford Road, Petersfield,
Hampshire GU32 3QB, United Kingdom
PLIVA
POM
PL 10622/0331 PA 585/33/2
xxxxx-C1
Bar code


BICALUTAMIDE
150MG
TABLETS


Bicalutamide 150mg Film-coated Tablets
30 Film-coated Tablets
Bicalutamide
150mg Film-coated Tablets
Bicalutamide
PLIVA
Each tablet contains
150mg bicalutamide
30 Film-coated Tablets
Bicalutamide 150mg Film-coated Tablets
30 Film-coated Tablets
Bicalutamide 150mg Film-coated Tablets
30 Film-coated Tablets
Batch no:
EXP date:
Contains lactose.
See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store below 30°C.
Keep out of the reach and sight of children.
MA Holder: PLIVA Pharma Ltd,
Vision House, Bedford Road, Petersfield,
Hampshire GU32 3QB, United Kingdom
PLIVA
POM
PL 10622/0331 PA 585/33/2
xxxxx-C1
Bar code




Bicalutamide 150mg Film-coated Tablets
40 Film-coated Tablets
Bicalutamide
150mg Film-coated Tablets
Bicalutamide
PLIVA
Each tablet contains
150mg bicalutamide
40 Film-coated Tablets
Bicalutamide 150mg Film-coated Tablets
40 Film-coated Tablets
Bicalutamide
150mg Film-coated Tablets
40 Film-coated Tablets
Batch no:
EXP date
Contains lactose.
See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store below 30°C.
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MA Holder: PLIVA Pharma Ltd,
Vision House, Bedford Road, Petersfield,
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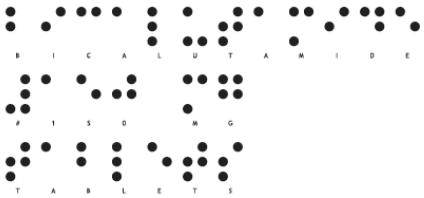
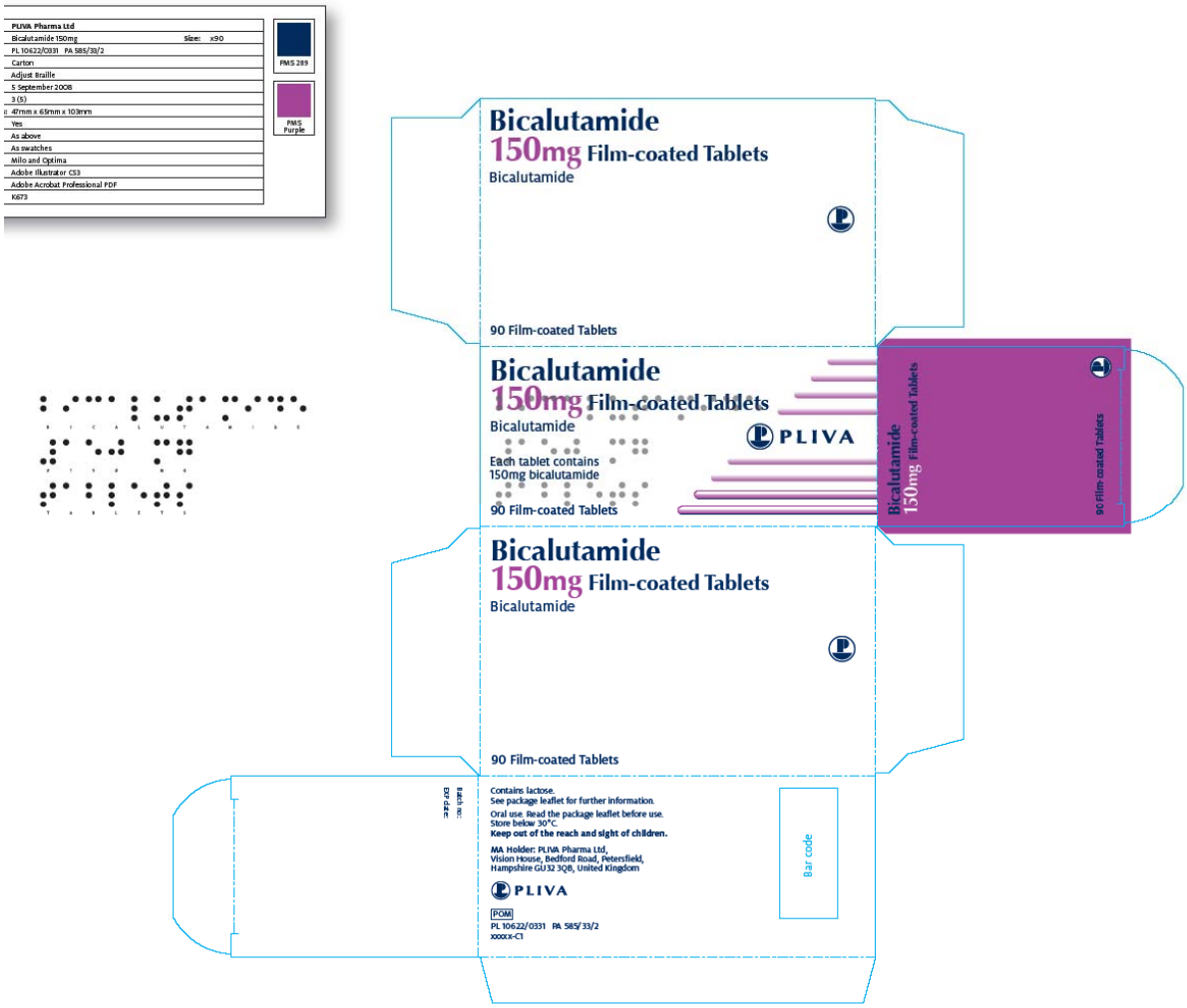
PLIVA
POM
PL 10622/0331 PA 585/33/2
xxxxx-C1
Bar code




PLIVA Pharma Ltd
Bicalutamide 150mg
Size: x90
PL 10622/0331 PA 585/33/2
Carton
Adjust Braille
5 September 2008
3 (5)
47mm x 65mm x 103mm
Yes
As above
As swatches
Milo and Optima
Adobe Illustrator CS3
Adobe Acrobat Professional PDF
K673
PMS 289
PMS Purple
Bicalutamide
150mg Film-coated Tablets
Bicalutamide
90 Film-coated Tablets
Bicalutamide
150mg Film-coated Tablets
Bicalutamide
PLIVA
Each tablet contains
150mg bicalutamide
90 Film-coated Tablets
Bicalutamide
150mg Film-coated Tablets
90 Film-coated Tablets
Bicalutamide
150mg Film-coated Tablets
Bicalutamide
90 Film-coated Tablets
Contains lactose.
See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store below 30°C.
Keep out of the reach and sight of children.
MA Holder: PLIVA Pharma Ltd,
Vision House, Bedford Road, Petersfield,
Hampshire GU32 3QB, United Kingdom
PLIVA
POM
PL 10622/0331 PA 585/33/2
xxxxx-C1
Bar code

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 50mg and 150mg film-coated tablets, in the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration, could be approvable.

These decentralised applications concern generic versions of bicalutamide submitted under Article 10.1 of Directive 2001/83/EC (as amended), a so called' 'Generic application'. However, in those CMS's where particular strengths of reference product are not authorised (IE – 150mg), the applications are submitted under article 10(3) 'hybrid'. The originator product is Casodex® 50 mg and 150mg Tablets by AstraZeneca UK Ltd, registered in the EU since 23rd February 1995.

With UK as the Reference Member State in these Decentralised Procedures, Pliva Pharma Limited is applying for the Marketing Authorisations for Bicalutamide 50 mg in CZ, DE, EE, HU, IE, LT, LV, PL, SI, and SK and for 150mg film-coated tablets in, CZ, DE, HU, IE, PL, SI, and SK

Bicalutamide is a non-steroidal antiandrogen, which binds to androgen receptors in the prostate and prevents the physiological effects of dihydrotestosterone. Bicalutamide 50 mg and 150mg 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.

Assurance has been provided of compliance to GCP for the clinical trial site.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Bicalutamide 50mg and 150mg Film-Coated Tablet
Name(s) of the active substance(s) (INN)	bicalutamide
Pharmacotherapeutic classification (ATC code)	Anti-androgens (L02 BB03)
Pharmaceutical form and strength(s)	50mg and 150mg Film-Coated Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1245/01-02/DC
Reference Member State	United Kingdom
Member States Concerned	50mg: CZ, DE, EE, HU, IE, LT, LV, PL, SI, and SK 150mg: CZ, DE, HU, IE, PL, SI, and SK
Marketing Authorisation Number(s)	PL 10622/0330-1
Name and address of the authorisation holder	PLIVA Pharma Limited, Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB – United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

Active substance

INN: Bicalutamide

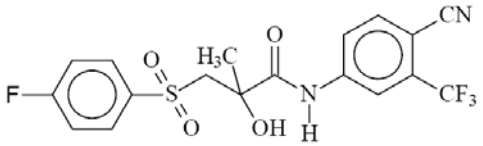
Chemical Name: (±)-N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)-sulfonyl]-2-hydroxy-2-methylpropanamide

Molecular formula: $C_{18}H_{14}F_4N_2O_4S$

M_r: 430.37

Description: White or creamy white crystalline powder

Structure:



Description: White or creamy white crystalline powder

Molecular formula: $C_{18}H_{14}F_4N_2O_4S$

M_r: 430.37

Chemical Name: (±)-N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)-sulfonyl]-2-hydroxy-2-methylpropanamide

Melting range: 189 °C to 195 °C

pH (0.5 % w/v) 2.0 to 3.0

CAS Number: 90357-06-5

Chirality: Bicalutamide has one asymmetric carbon atom; the possible numbers of the optical isomers is two. The active substance is the racemic mixture of two enantiomers. The R enantiomer is primarily responsible for the anti-androgenic activity. The optical rotation is not considered relevant.

Solubility: Soluble in THF and acetone.

This is subject to DMF. A letter of access has been provided

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 specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active bicalutamide is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Acceptable justification of the proposed specifications are provided.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Stability studies have been performed with acceptable re-test period.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely croscarmellose sodium, sodium Laurilsulfate, povidone K25, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, Opadry II 31F58914 White and Purified Water. All excipients used comply with their respective European Pharmacopoeia monograph with the exception of Opadry II 31F58914 White which complies with in house specification. Satisfactory certificates of analysis have been provided for all excipients.

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

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce Bicalutamide Film-coated Tablets that could be considered as generic products to the originator product Casodex.

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

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

Manufacture

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

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished product specification
The finished product specification is satisfactory. 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 working standards used.

Container Closure System
Product is packaged in to PVC Aluminium blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage condition 'Store below 30 degrees C' is proposed. This is acceptable.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.

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.

Conclusion
The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence. Similar dissolution profiles have been demonstrated for the proposed and reference products. It is recommended that Marketing Authorisations should be granted for these applications.

PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic products. The non-clinical overview provides a reasonable review of the known pharmacological and toxicological properties of Bicalutamide.

CLINICAL ASPECTS

1. INTRODUCTION

These decentralised applications concern a generic version of Bicalutamide, submitted under article 10(1) of Directive 2001/83/EC (as amended), a so called 'Generic Application'. However, in those CMS's where particular strengths of reference product are not authorised (IE – 150mg), the applications are submitted under article 10(3) 'hybrid'. The reference product is Casodex Tablets 50 mg and 150 mg, AstraZeneca UK Limited, authorised in the UK since the 23rd of February, 1995. The reference product has been authorised in the EEA for at least 10 years.

2. BACKGROUND

Bicalutamide is an anti-androgen, which binds to androgen receptors in the prostate and blocks the stimulatory action of androgens, preventing the physiological effects of dihydrotestosterone (DHT). Regression of prostatic tumours results from this inhibition. Bicalutamide is a racemate, its anti-androgenic activity being almost exclusively exhibited by the R-enantiomer. Bicalutamide 50 mg Tablets are indicated for the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration. Bicalutamide 150 mg Tablets are indicated either alone or as adjuvant to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer at high risk for disease progression. Common adverse events include hot flushes, breast tenderness, diarrhoea and nausea.

3. INDICATIONS

Treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration.

4. DOSE & DOSE SCHEDULE

See the SPC for full details. The recommended dosages and dose schedules are consistent with the reference product.

5. CLINICAL PHARMACOLOGY

To support the application, the Applicant has submitted two bioequivalence studies, one for the 50 mg and one for the 150mg film-coated tablets.

Efficacy Studies

No new efficacy data have been submitted and none are required for these generic applications.

Bioequivalence Study: 50 mg Tablets.

The study was an open-label, single-dose, randomized, 2-way crossover, 2-sequence design. The aim of the study was to compare two bicalutamide formulations (each tablet containing 50 mg of bicalutamide). The study was conducted in compliance with Good Laboratory Practice and the ICH guidelines regarding Good Clinical Practice.

Twenty healthy male subjects, aged between 21 and 54, received either one tablet of the test or reference product in a fasted state. All subjects enrolled in the study satisfied the inclusion/exclusion criteria as listed in the protocol. The test product (A) was Bicalutamide 50 mg tablets (Pliva-Lachema a.s., Czech Republic) and the reference product (B) Casodex Bicalutamide 50 mg tablets (AstraZeneca UK Ltd). Blood samples were collected at the

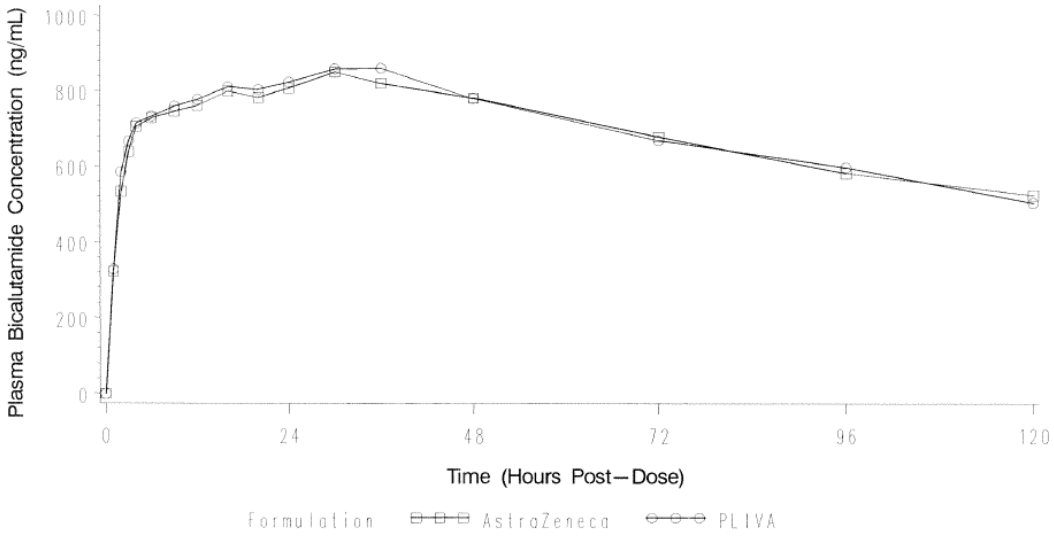
following time points 0 (pre-dose); 1 ; 2 ; 3 ; 4 ; 6; 9 ; 12 ; 16 ; 20 ; 24 ; 30; 36; 48; 72; 96; 120 hours after the dose. Plasma levels of bicalutamide were determined using a validated LC/MS/MS method. The analytical range for bicalutamide in plasma was 10.0 - 5000 ng/mL. There was an 8-week washout interval between the 2 dose administrations. Analyses of variance were performed on the ln-transformed PK parameters AUC_{0-120} and C_{max}.

Results

A total of 20 subjects were dosed. All 20 subjects completed the study. The mean age of the subjects was 35 years (range of 21 - 54 years).

The results for the pharmacokinetic parameters for the 50 mg tablet are illustrated below.

Figure 2
Project No. AA34725
Mean Plasma Bicalutamide Concentrations
(Linear Plot)



Treatment	AUC_{0-120} ng.hr/ml	C_{max} ng/ml	T_{max} hr
Test (Mean)	**82812.51**	**898.714**	**26.550**
Reference (Mean)	**81790.47**	**867.661**	**28.400**
***Ratio (90% CI)**	**96-106**	**100-108**	

Both the test and reference dosage forms have essentially similar pharmacokinetic parameters in terms of AUC_{0-120} and C_{max} for Bicalutamide. The log transformed 90% CI ranges for AUC was 96-106 %. For C_{max} the 90% CI range was 100-108%.

Conclusion on Bioequivalence

The 90% confidence intervals for AUC_{0-120} and C_{max} lie within the acceptance NfG on the investigation of bioavailability and bioequivalence. Therefore, the Test product 50 mg Bicalutamide was shown to be bioequivalent to the Reference product.

Adverse Events (AE's): Safety
There were no deaths or serious adverse events during the study. Two subjects (10.0% of the study population) experienced at least 1 adverse event that was possibly, probably, or definitely related to the test product whilst no subjects experienced any adverse events related to Reference.

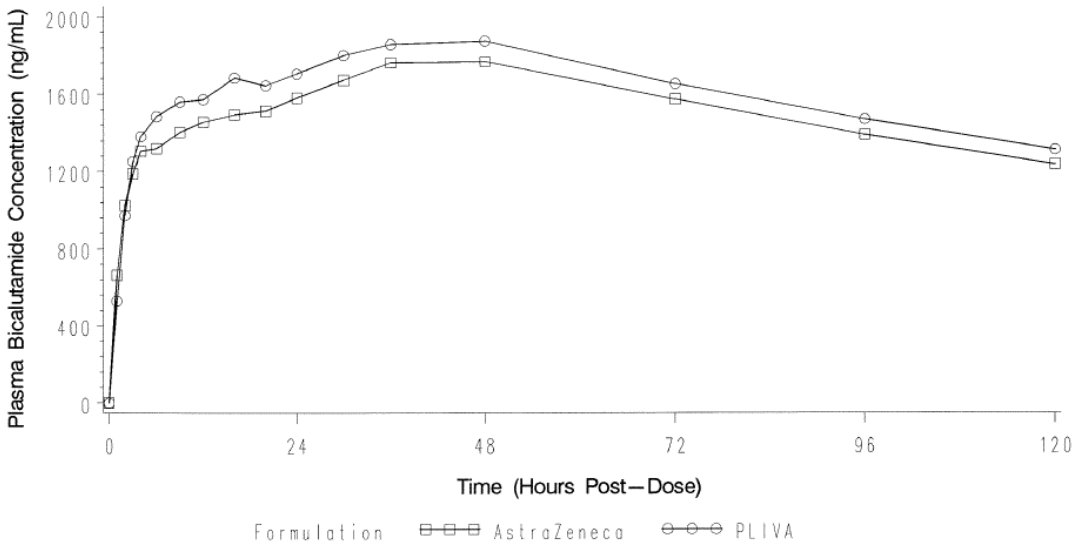
Bioequivalence Study: 150 mg Tablet
The study was an open-label, single-dose, randomized, 2-way crossover, 2-sequence design. The aim of the study was to compare two bicalutamide formulations (each tablet containing 150 mg of bicalutamide). The study was conducted in compliance with Good Laboratory Practice and the ICH guidelines regarding Good Clinical Practice.

Twenty healthy male subjects, aged between 21 and 55, received either one tablet of the test or reference product in a fasted state. All subjects enrolled in the study satisfied the inclusion/exclusion criteria as listed in the protocol. The test product (A) was Bicalutamide 150 mg tablets (Pliva-Lachema a.s., Czech Republic) and the reference product (B) Casodex Bicalutamide 150 mg tablets (AstraZeneca UK Ltd). Blood samples were collected at the following time points 0 (pre-dose); 1 ; 2 ; 3 ; 4 ; 6; 9 ; 12 ; 16 ; 20 ; 24 ; 30; 36; 48; 72; 96; 120 hours after the dose. Plasma levels of bicalutamide were determined using a validated LC/MS/MS method. The analytical range for bicalutamide in plasma was 10.0-5000 ng/mL. There was an 8-week washout interval between the 2 dose administrations. Analyses of variance were performed on the ln-transformed PK parameters AUC $_{0\text{-}120}$ and C_{max}.

Results
A total of 20 subjects were dosed. All 20 subjects completed the study. The mean age of the subjects was 37 years (range of 21 - 55 years).

The results for the pharmacokinetic parameters for the 150 mg tablet are illustrated below.

Figure 2
Project No. AA40129
Mean Plasma Bicalutamide Concentrations
(Linear Plot)



Treatment	AUC_{0-120} ng.hr/ml	C_{max} ng/ml	T_{max} hr
Test (Mean)	**187959.13**	**1916.65**	**38.85**
Reference (Mean)	**177829.17**	**1794.33**	**36.6**
*Ratio (90% CI)	**100-112**	**101-113**	

Both the test and reference dosage forms have essentially similar pharmacokinetic parameters in terms of AUC_{0-120} and C_{max} for Bicalutamide. The log transformed 90% CI ranges for AUC was 100-112 %. For C_{max} the 90% CI range was 101-113%.

Conclusion on Bioequivalence
The 90% confidence intervals for AUC_{0-120} and C_{max} lie within the acceptance NfG on the investigation of bioavailability and bioequivalence. Therefore, the Test product 150 mg Bicalutamide was shown to be bioequivalent to the Reference product.

Assessor's comment:
The results of the study demonstrate bioequivalence between the Test product, Bicalutamide 150 mg Tablets and the Reference product, Casodex 150 mg Tablets, at least up to 120 hours post dosing. The confidence intervals for AUC and C_{max} fall within the acceptance criteria ranges of 80-125%, in line with current guidelines.

Adverse Events (AE's): Safety
There were no deaths or serious adverse events during the study. One subject (5.0% of the study population) experienced at least 1 adverse event that was possibly, probably, or definitely related to the test product and one subject experienced at least 1 adverse event that were possibly, probably, or definitely related to the reference product.

Pharmacokinetic studies

Pharmacodynamic studies

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

The pharmacodynamic and pharmacokinetic claims in the SPC are consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties have been extensively studied in the past.

Post marketing experience
No post-marketing data is available. The medicinal product has not been marketed in any country.

Bicalutamide has a well-recognised efficacy and an acceptable level of safety in the indications approved for Bicalutamide 50 mg and 150 mg Tablets, and corresponding products have been widely used in many countries. Overall the risk: benefit analysis for Bicalutamide 50mg and 150 mg Tablets is considered favourable and approval is recommended.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome