Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Bicalutamide 50mg Film-Coated Tablets
Bicalutamide 150mg Film-Coated Tablets

UK/H/1270/001-2/DC

UK licence no: PL 19070/0003-4

ICN Polfa Rzeszow SA

Bicalutamide 50mg Film-Coated Tablets
Bicalutamide 150mg Film-Coated Tablets

LAY SUMMARY

On 9th October 2008, the MHRA granted ICN Polfa Rzeszow SA Marketing Authorisations (licences) for the medicinal products Bicalutamide 50mg and 150mg Film-Coated Tablets (PL 19070/0003-4; UK/H/1270/001-2/DC). These are prescription only medicines for the treatment of advanced prostate cancer (50mg) and prostate cancer where the cancer has spread from the capsule of the prostate gland to the close surrounding tissue (150mg).

The active ingredient, bicalutamide, belongs to a group of medicines called non-steroidal anti-androgens. It blocks the undesired effect of a chemical made by a male sex gland (androgens) and inhibits cell growth in the prostate in this way.

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 Film-Coated Tablets Bicalutamide 150mg Film-Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Bicalutamide
Form	Film-Coated Tablets
Strength	50 and 150mg Film-Coated Tablets
MA Holder	ICN Polfa Rzeszów S.A., 2 Przemysłowa Street, 35-959 Rzeszów – Poland
RMS	UK
CMS	Czech Republic, Hungary, Poland and the Slovak Republic
Procedure Number	UK/H/1270/001-2/DC
Timetable	Day 210 – 1st September 2008

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Bicalutamide 50 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains 50 mg bicalutamide.
Excipient(s): Each tablet contains 62.7 mg of lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
White, round, biconvex film-coated tablets, with diameter of 6.5 mm..

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 film coated tablet (50mg) daily with or without food.

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 50 mg 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 < 30 ml/min)

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

4.3 Contraindications
Bicalutamide 50 mg is contra-indicated in women, children and adolescents.

Bicalutamide 50 mg is contraindicated in patients hypersensitivity to the active substance or any of the excipients.

Co-administration of terfenadine, astemizole or cisapride with Bicalutamide 50 mg is contra-indicated.

4.4 Special warnings and precautions for use
Initiation of treatment should be under the direct supervision of a specialist and subsequently patients should be kept under regular surveillance.

Bicalutamide is extensively metabolised in the liver. Research results 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.

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

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.

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.

Bicalutamide 50 mg 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 pharmacological or pharmacokinetic interactions have been demonstrated between bicalutamide and LHRH analogues.

In vitro studies have shown that the 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 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 contra-indicated.

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 cyclosporine, 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 processes 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 site. 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

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

The following undesirable effects may occur during treatment with Bicalutamide 50 mg.

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Very rare (<1/10,000)
General disorders and administration site conditions	Hot flushes	Asthenia			
Reproductive system and breast disorders	Gynaecomastia, breast tenderness. May be reduced by concomitant castration. The majority of patients receiving bicalutamide 150 mg as monotherapy experience gynaecomastia and/or breast pain. In studies these symptoms were considered to be severe in up to 5% of the patients. Gynaecomastia may not resolve spontaneously following cessation of therapy, particularly after prolonged treatment.				
Skin and subcutaneous tissue disorders		Pruritus		Dry skin	
Gastrointestinal disorders		Diarrhoea, nausea		Vomiting	
Hepatobiliary disorders		Hepatic changes (elevated levels of transaminases, bilirubinaemia cholestasis and jaundice), hepatomegaly. These changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4).			Hepatic failure has occurred rarely in patients treated with bicalutamide but a causal relationship has not been established with certainty. Periodic liver function testing should be considered (see section 4.4).
Respiratory, thoracic and mediastinal disorders			Interstitial lung disease		
Renal and urinary disorders			Haematuria		
Immune system disorders			Hypersensitivity reactions, including angio-oedema and urticaria		
Psychiatric disorders			Depression		

In addition the following adverse experiences were reported in clinical trials during treatment with bicalutamide with/without a LHRH analogue:					
System organ class	Very common	Common	Uncommon	Rare	Very rare
Reproductive system and breast disorders	Decreased libido, erectile dysfunction, impotence				
General disorders and administration site conditions		Oedema, general pain, pelvic pain, chills	Abdominal pain, chest pain, headache, pain in the back, neck pain		
Skin and subcutaneous tissue disorders		Rash, sweating, hirsutism	Alopecia		
Gastrointestinal disorders		Constipation	Dry mouth, dyspepsia, flatulence		
Nervous system disorders		Dizziness, insomnia	Somnolence		
Metabolism and nutrition disorders		Weight gain, diabetes mellitus	Anorexia, hyperglycaemia , weight loss		
Blood and lymphatic system disorders		Anaemia			Thrombocytopenia
Renal and urinary disorders			Nocturia		
Respiratory, thoracic and mediastinal disorders			Dyspnoea		
Cardiac disorders					Heart failure, angina, conduction defects including PR and QT interval prolongations, arrhythmias and non-specific ECG changes

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 may not be helpful, since bicalutamide is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormone antagonists and related agents, antiandrogens, ATC code: L02BB03.

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 of Bicalutamide.

A dosing scheme of 50mg 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 for subjects with severe hepatic impairment, the (R)-enantiomer is more slowly eliminated from plasma.

Bicalutamide is highly protein bound (racemate to 96%, R-enantiomer > 99%) 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 liver. Target organs 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. This enzyme induction observed in animals has not been found in humans. 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:
Lactose monohydrate
Povidone K- 25
Sodium starch glycolate Type A
Magnesium Stearate
Film-Coating:
Opadry OY-S-9622 consisting of:
Hypromellose 5 cP (E464)
Titanium dioxide (E171)
Propylene Glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters
28 tablets contained in a carton.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

ICN Polfa Rzeszów S.A.
2 Przemysłowa Street,
35-959 Rzeszów, Poland

8 MARKETING AUTHORISATION NUMBER(S)
PL 19070/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/10/2008

10 DATE OF REVISION OF THE TEXT
09/10/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide 150 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 150 mg bicalutamide.
Excipient(s): Each tablet contains 188.0 mg of lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White, round, biconvex, film coated tablets, with diameter of 10.5mm, and a score line on one side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bicalutamide 150 mg 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 film coated tablet (50mg) daily with or without food.

Route: Oral

The tablets should be swallowed whole with liquid.

Treatment with Bicalutamide should be taken continuously for at least 2 years or until disease progression.

Children and adolescents: Bicalutamide 50 mg 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 < 30 ml/min) (see Section 4.4)

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

4.3 Contraindications

Bicalutamide 150 mg is contra-indicated in women, children and adolescents.

Bicalutamide 150 mg is contraindicated in patients with hypersensitivity to the active substance or any of the excipients.

Co-administration of terfenadine, astemizole or cisapride with Bicalutamide 150 mg is contra-indicated (see Section 4.5).

4.4 Special warnings and precautions for use

Bicalutamide is extensively metabolised in the liver. Research results 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.

Severe hepatic changes have been observed rarely with Bicalutamide 150mg (see Section 4.8). Bicalutamide therapy should be discontinued if changes are severe.

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.
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.

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

Bicalutamide 150 mg 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 the 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 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 contra-indicated.

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 cyclosporine, 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 processes 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 site. 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

The pharmacological action of bicalutamide may give rise to certain undesirable effects. These include the following:

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Very rare (<1/10,000)
General disorders and administration site conditions	Hot flushes	Asthenia			
Reproductive system and breast disorders	Gynaecomastia, breast tenderness. May be reduced by concomitant castration. The majority of patients receiving bicalutamide 150 mg as monotherapy experience gynaecomastia and/or breast pain. In studies these symptoms were considered to be severe in up to 5% of the patients. Gynaecomastia may not resolve spontaneously following cessation of therapy, particularly after prolonged treatment.				
Skin and subcutaneous tissue disorders		Pruritus		Dry skin	
Gastrointestinal disorders		Diarrhoea, nausea		Vomiting	
Hepatobiliary disorders		Hepatic changes (elevated levels of transaminases, bilirubinaemia cholestasis and jaundice), hepatomegaly. These changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4).			Hepatic failure has occurred rarely in patients treated with bicalutamide but a causal relationship has not been established with certainty. Periodic liver function testing should be considered (see section 4.4).
Respiratory, thoracic and mediastinal disorders			Interstitial lung disease		
Renal and urinary disorders			Haematuria		
Immune system disorders			Hypersensitivity reactions, including angio-oedema and urticaria		
Psychiatric disorders			Depression		

In addition the following adverse experiences were reported in clinical trials during treatment with bicalutamide with/without a LHRH analogue:					
System organ class	Very common	Common	Uncommon	Rare	Very rare
Reproductive system and breast disorders	Decreased libido, erectile dysfunction, impotence				
General disorders and administration site conditions		Oedema, general pain, pelvic pain, chills	Abdominal pain, chest pain, headache, pain in the back, neck pain		
Skin and subcutaneous tissue disorders		Rash, sweating, hirsutism	Alopecia		
Gastrointestinal disorders		Constipation	Dry mouth, dyspepsia, flatulence		
Nervous system disorders		Dizziness, insomnia	Somnolence		
Metabolism and nutrition disorders		Weight gain, diabetes mellitus	Anorexia, hyperglycaemia , weight loss		
Blood and lymphatic system disorders		Anaemia			Thrombocytopenia
Renal and urinary disorders			Nocturia		
Respiratory, thoracic and mediastinal disorders			Dyspnoea		
Cardiac disorders					Heart failure, angina, conduction defects including PR and QT interval prolongations, arrhythmias and non-specific ECG changes

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 may not be helpful, since bicalutamide is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormone antagonists and related agents, antiandrogens, ATC code: L02BB03.

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.

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

Bicalutamide (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 3 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 patient groups but was most evident in those at highest risk of disease progression. Therefore, clinicians may decide that the optimum medical strategy for a patient at low risk of disease progression, particularly in the adjuvant setting following radical prostatectomy, may be to defer hormonal therapy until signs that the disease is progressing.

No overall survival difference was seen at 7.4 years median follow up with 22.9% mortality (HR=0.99; 95% 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:

Table 1 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)

Table 2 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 to 1.37). In view of this, the benefit-risk profile for the use of bicalutamide is not considered favourable in this group of patients

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 accumulates to about 10 fold in plasma as compared to the levels measured after a single dose of 50mg of Bicalutamide.

A dosing scheme of 150mg Bicalutamide daily will result in a steady-state concentration of the R-enantiomer of 22 microgram/ml and as a consequence of its 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 for subjects with severe hepatic impairment, the (R)-enantiomer is more slowly eliminated from plasma.

Bicalutamide is highly protein bound (racemate 96%, R-enantiomer > 99%) and extensively metabolised (via 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)-bicalutamide in semen of men receiving bicalutamide 150 mg 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 liver. This enzyme induction observed in animals 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. -None of these findings in preclinical testing are considered to have relevance to the treatment of patients with advanced prostate cancer.

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

Genotoxicity studies did not reveal any mutagenic potential of bicalutamide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Povidone K- 25
Sodium starch glycolate Type A
Magnesium Stearate
Film-Coating:
Opadry OY-S-9622 consisting of:
Hypromellose 5 cP (E464)
Titanium dioxide (E171)
Propylene Glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters
28 tablets contained in a carton.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

ICN Polfa Rzeszów S.A.
2 Przemysłowa Street,
35-959 Rzeszów, Poland

8 MARKETING AUTHORISATION NUMBER(S)

PL 19070/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/10/2008

10 DATE OF REVISION OF THE TEXT
09/10/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Bicalutamide, 50 mg, film-coated tablets
Bicalutamide

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

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

1. WHAT BICALUTAMIDE 50 MG IS AND WHAT IT IS USED FOR

Bicalutamide 50 mg is used for the treatment of advanced prostate cancer. It is taken together with a drug known as an luteinising hormone-releasing hormone (LHRH) analogue which reduces the levels of androgens (male sex hormones) within the body, or with accompanying surgical removal of the testicles. The active ingredient of Bicalutamide 50 mg, bicalutamide, belongs to a group of medicines called non-steroidal anti-androgens. It 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 50 MG

Do not take Bicalutamide 50 mg
- if you are allergic (hypersensitive) to bicalutamide or any of the other ingredients of Bicalutamide 50 mg
- if you are already taking terfenadine or astemizole (for hay fever or allergy), or cisapride (for stomach disorders).

Bicalutamide 50 mg should not be taken by women or must not be given to children or adolescents.

Take special care with Bicalutamide 50 mg
- 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. If severe disturbances to liver function develop, treatment with Bicalutamide 50 mg should be discontinued.
- if your renal function 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 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.
If you take Bicalutamide 50 mg 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 50 mg:

- warfarin or any similar medicine to prevent blood clots,
- terfenadine or astemizole (for hay fever or allergy),
- cisapride (for stomach disorders),
- ciclosporin (used to suppress your immune system to prevent and treat rejection of a transplanted organ or bone marrow),
- calcium channel blockers (used to treat high blood pressure or some heart conditions)
- cimetidine (used to treat stomach ulcers),
- ketoconazole (used to treat fungal infections of the skin and nails).

Taking Bicalutamide 50 mg with food and drink
Bicalutamide 50 mg can be taken before, during or after a meal, but also you can take them without food. The film-coated tablet should be swallowed with some water or another liquid.

Pregnancy and breast-feeding
Bicalutamide 50 mg is contra-indicated in females and must not be given to pregnant or breast-feeding mothers.

Driving and using machines
Bicalutamide 50 mg is unlikely to adversely affect your ability to drive a car or to operate machinery. However, some people may occasionally feel dizzy or drowsy after taking Bicalutamide 50 mg. If this happens to you, you should exercise caution when carrying out such tasks. If you suffer from dizziness or drowsiness you would be best advised not to carry out such tasks. However if you still drive a car or use machines you should exercise extra caution.

Important information about some of the ingredients of Bicalutamide 50 mg
Bicalutamide 50 mg contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor immediately.

3. HOW TO TAKE BICALUTAMIDE 50 MG

Always take Bicalutamide 50 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is one film-coated tablet daily. It is better to take the film-coated tablet at the same time every day. The film-coated tablet should be swallowed with some water or another liquid without being chewed and can be taken with or without food.

Children and adolescents
This medicine is not recommended for patients under the age of 18 years.

If you take more Bicalutamide 50 mg than you should
If you take more than your normal dose, contact your doctor. In the case of an overdose, contact the nearest hospital immediately. If possible, take your film-coated tablets or the box with you to show the doctor what you have taken.

If you forget to take Bicalutamide 50 mg
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 dose. If you are worried, ask your doctor or pharmacist for advice.

If you stop taking Bicalutamide 50 mg
Do not stop taking your film-coated tablets, even if you are feeling well, unless your doctor tells you.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines Bicalutamide 50 mg can cause side effects, although not everybody gets them.

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

Contact your doctor or seek medical help immediately if you experience any of the following serious side effects
Very rare (estimated frequency is less than 1 person out of 10,000):
- Liver failure
- Chest pain (angina) and heart failure (which may be associated with breathlessness, especially on exertion, a fast heart beat, swelling in the limbs and mottling of the skin), irregular heart beat (arrythmia), abnormal ECG heart tracing.
- Reduction in blood platelets which increases the risk of bleeding or bruising (thrombocytopenia).

Uncommon serious side effects (affecting less than 1 in 100 people):
- Serious allergic reaction which causes swelling of the face, lips, tongue and/or throat, which may cause difficulties in swallowing or breathing or severe itching of the skin with raised lumps.
- Serious breathlessness or sudden worsening of breathlessness, possibly with a cough or fever. Some patients taking Bicalutamide get an inflammation of the lungs called interstitial lung disease.

The following side effects are possible for Bicalutamide 50 mg:
Side effects that are very common (estimated frequency is more than 1 person out of 10):
– tender or enlarged breast tissue
– hot flushes
– impotence (erectile dysfunction), reduced sex drive

Side effects that are common (estimated frequency is less than 1 person out of 10 but more than 1 out of 100):
- diarrhoea
- itching
- feeling weak
- sleeplessness
- having frequent loose or liquid bowel movements
- liver changes
- chills, general pain and swelling
- sweating
- constipation
- weight gain
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- dizziness
- pelvic pain
- rash
- nausea
- excessive hair growth
- diabetes mellitus

Side effects that are uncommon (estimated frequency is less than 1 person out of 100 but more than 1 out of 1000):
- indigestion
- depression
- hair loss
- weight loss
- allergic reactions
- breathlessness, or sudden worsening of breathlessness
- abdominal pain
- drowsiness
- needing to urinate during the night
- blood in urine
- inflammation of the lungs called interstitial lung disease
- chest pain
- neck pain
- headache
- dry mouth
- flatulence
- Anorexia
- Hyperglycaemia (high blood sugar levels)
- severe itching of the skin (with raised lumps) or swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing.

Rare side effects (estimated frequency is less than 1 person out of 1000 but more than 1 out of 10,000):
- vomiting
- dry skin

Occasionally, Bicalutamide 50 mg may be associated with changes in your blood which may require your doctor to do certain blood tests.
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE BICALUTAMIDE 50 MG

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

Do not use Bicalutamide 50 mg after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

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

6. FURTHER INFORMATION

What Bicalutamide 50 mg contains
– The active substance is bicalutamide. Each film-coated tablet contains 50mg bicalutamide.
The other ingredients are:
Tablet core:
Lactose monohydrate, Povidone K- 25, Sodium starch glycolate Type A, Magnesium Stearate.

Film coating:
Opadry OY-S-9622 which contains Hypromellose 5cP (E464), Titanium dioxide (E171) and Propylene Glycol.

What Bicalutamide 50 mg looks like and contents of the pack
Bicalutamide 50 mg is supplied as white, round, biconvex film-coated tablets. The film-coated tablets are packed in blister packs containing 28 film-coated tablets contained in a carton.

Marketing Authorisation Holder
ICN Polfa Rzeszów S.A.
2 Przemysłowa Street
35-959 Rzeszów, Poland

Manufacturer
ICN Polfa Rzeszów S.A.
2 Przemysłowa Street
35-959 Rzeszów
Poland
&
Genepharm S.A
18th klm Marathonos Avenue,
153 51 Pallini Attikis
Greece

This medicinal product is authorised in the Member States of the EEA under the following names:
UK:
Bicalutamide, 50 mg, film-coated tablets
PL:
Prostide, 50 mg, tabletki powlekane
HU:
Grommar, 50 mg, filmtabletta
SK:
Glanuta, 50 mg, filmom obalené tablety
CZ:
Glanuta, 50 mg, potahované tablety

This leaflet was last approved in August 2008

PACKAGE LEAFLET: INFORMATION FOR THE USER

Bicalutamide, 150 mg, film-coated tablets
Bicalutamide

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

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

1. WHAT BICALUTAMIDE 150 MG IS AND WHAT IT IS USED FOR

Bicalutamide 150 mg can be used alone but can also be given as part of a combination treatment to patients that have had their prostate removed. Additionally in combination with radiation therapy for the treatment of prostate cancer, whereby the cancer has spread from the capsule of the prostate gland to the close surrounding tissue. These patients are at high risk for the cancer to spread.

The active ingredient of Bicalutamide 150 mg, bicalutamide, belongs to a group of medicines called non-steroidal anti-androgens. It blocks the undesired effect of a chemical made by a male sex gland (androgens) and inhibits cell growth in the prostate in this way.

2. BEFORE YOU TAKE BICALUTAMIDE 150 MG

Do not take Bicalutamide 150 mg
- if you are allergic (hypersensitive) to bicalutamide or any of the other ingredients of Bicalutamide 150 mg
- if you are already taking terfenadine or astemizole (for hay fever or allergy), or cisapride (for stomach disorders).

Bicalutamide 150 mg should not be taken by women or must not be given to children or adolescents.

Take special care with Bicalutamide 150 mg
- 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. 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.
- if you suffer from heart disease. If this is the case, your doctor should regularly monitor your heart function.
- if your blood still shows high levels of a certain protein used to detect prostate cancer and the disease is still getting worse, bicalutamide treatment may need to be stopped.

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.

If you take Bicalutamide 150 mg 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 150 mg:

- warfarin or any similar medicine to prevent blood clots,
- terfenadine or astemizole (for hay fever or allergy),
- cisapride (for stomach disorders),
- ciclosporin (used to suppress your immune system to prevent and treat rejection of a transplanted organ or bone marrow),
- calcium channel blockers (used to treat high blood pressure or some heart conditions)
- cimetidine (used to treat stomach ulcers),
- ketoconazole (used to treat fungal infections of the skin and nails).

Taking Bicalutamide 150 mg with food and drink
Bicalutamide 150 mg can be taken before, during or after a meal, but also you can take them without food. The film-coated tablet should be swallowed with some water or another liquid.

Pregnancy and breast-feeding
Bicalutamide 150 mg is contra-indicated in females and must not be given to pregnant or breast-feeding mothers.

Bicalutamide 150 mg may induce a period of subfertility or infertility in man.

Driving and using machines
Bicalutamide 150 mg is unlikely to adversely affect your ability to drive a car or to operate machinery. However, some people may occasionally feel dizzy or drowsy after taking Bicalutamide 150 mg. If you suffer from dizziness or drowsiness you would be best advised not to carry out such tasks. However if you still drive a car or use machines you should exercise extra caution.

Important information about some of the ingredients of Bicalutamide 150 mg
Bicalutamide 150 mg contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor immediately.

3. HOW TO TAKE BICALUTAMIDE 150 MG

Always take Bicalutamide 150 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is one film-coated tablet daily. It is better to take the tablet at the same time every day. The film-coated tablet should be swallowed with some water or another liquid without being chewed and can be taken with or without food.

Children and adolescents
This medicine is not recommended for patients under the age of 18 years.

If you take more Bicalutamide 150 mg than you should
If you take more than your normal dose, contact your doctor. In the case of an overdose, contact the nearest hospital immediately. If possible, take your film-coated tablets or the box with you to show the doctor what you have taken.

If you forget to take Bicalutamide 150 mg
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 dose. If you are worried, ask your doctor or pharmacist for advice.

If you stop taking Bicalutamide 150 mg
Do not stop taking your film-coated tablets, even if you are feeling well, unless your doctor tells you.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Bicalutamide 150 mg can cause side effects, although not everybody gets them.

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

Contact your doctor or seek medical help immediately if you experience any of the following serious side effects
Very rare (estimated frequency is less than 1 person out of 10,000):
- Liver failure
- Chest pain (angina) and heart failure (which may be associated with breathlessness, especially on exertion, a fast heart beat, swelling in the limbs and mottling of the skin), irregular heart beat (arrythmia), abnormal ECG heart tracing.
- Reduction in blood platelets which increases the risk of bleeding or bruising (thrombocytopenia).

Uncommon serious side effects (affecting less than 1 in 100 people):
- Serious allergic reaction which causes swelling of the face, lips, tongue and/or throat, which may cause difficulties in swallowing or breathing or severe itching of the skin with raised lumps.
- Serious breathlessness or sudden worsening of breathlessness, possibly with a cough or fever. Some patients taking Bicalutamide get an inflammation of the lungs called interstitial lung disease.

Tell your doctor if any of the following side effects bother you:
Side effects that are very common (estimated frequency is more than 1 person out of 10):
- tender or enlarged breast tissue
- hot flushes
- impotence (erectile dysfunction), reduced sex drive

Side effects that are common (estimated frequency is less than 1 person out of 10 but more than 1 out of 100):
- sleeplessness
- having frequent loose or liquid bowel movements
- liver changes
- chills, general pain and swelling
- sweating
- constipation
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- dizziness
- weight gain
- itching
- feeling weak
- nausea
- pelvic pain
- rash
- excessive hair growth
- diabetes mellitus

Side effects that are uncommon (estimated frequency is less than 1 person out of 100 but more than 1 out of 1000):
- indigestion
- depression
- hair loss
- weight loss
- allergic reactions
- breathlessness, or sudden worsening of breathlessness
- abdominal pain
- drowsiness
- needing to urinate during the night
- blood in urine
- inflammation of the lungs called interstitial lung disease
- chest pain
- back pain
- neck pain
- headache
- dry mouth
- flatulence
- Anorexia
- Hyperglycaemia (high blood sugar levels)
- severe itching of the skin (with raised lumps) or swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing

Side effects that are rare (estimated frequency is less than 1 person out of 1000 but more than 1 out of 10,000):
- dry skin
- vomiting

Occasionally, Bicalutamide 150 mg may be associated with changes in your blood, which may require your doctor to do certain blood tests.
If you notice any side effect not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE BICALUTAMIDE 150 MG

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

Do not use Bicalutamide 150 mg after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

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

6. FURTHER INFORMATION

What Bicalutamide 150 mg contains
– The active substance is bicalutamide. Each film-coated tablet contains 150 mg bicalutamide.
The other ingredients are:
Tablet core:
Lactose monohydrate, Povidone K- 25, Sodium starch glycolate Type A, Magnesium Stearate.

Film coating:
Opadry OY-S-9622 which contains Hypromellose 5cP (E464), Titanium dioxide (E171) and Propylene Glycol.

What Bicalutamide 150 mg looks like and contents of the pack
Bicalutamide 150 mg is supplied as white, round, biconvex film-coated tablets with a score line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal parts.
The film-coated tablets are packed in blister packs containing 28 film-coated tablets contained in a carton.

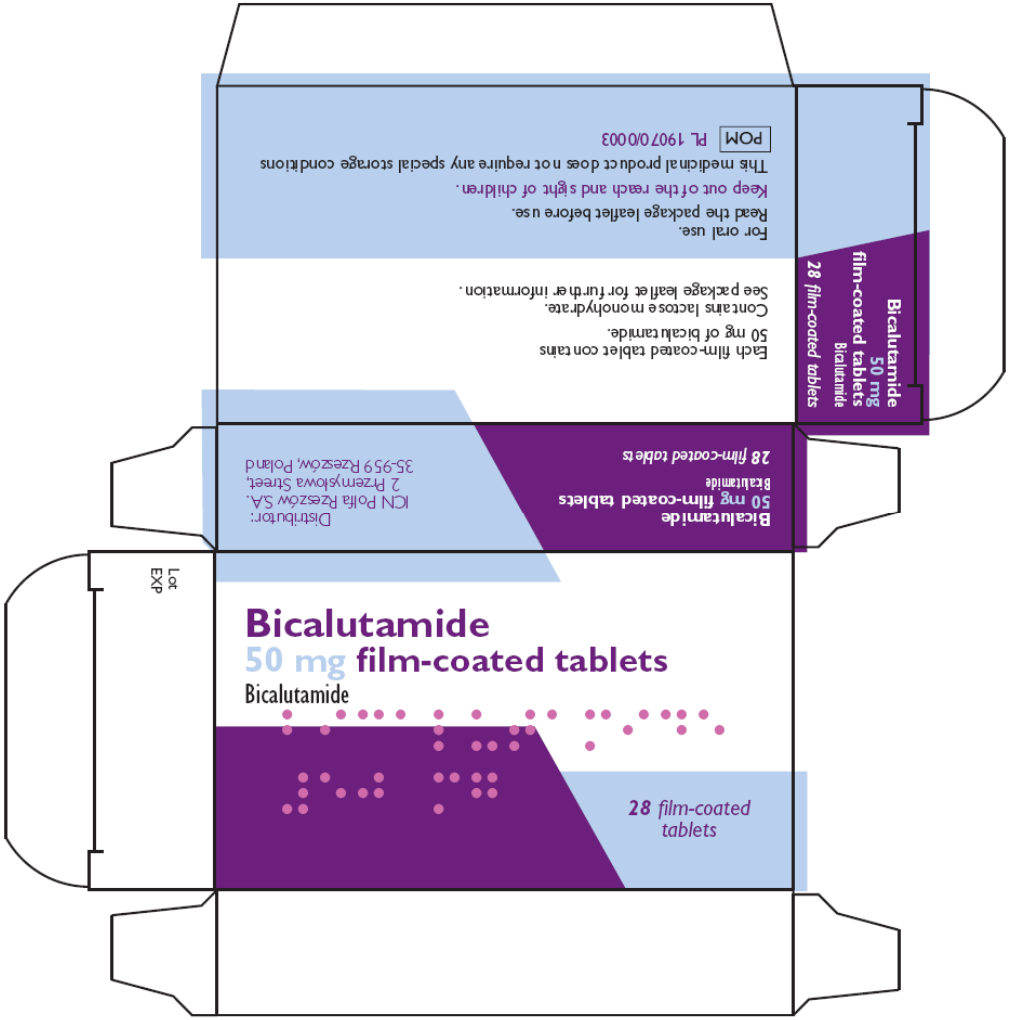
Marketing Authorisation Holder
ICN Polfa Rzeszów S.A.
2 Przemysłowa Street
35-959 Rzeszów, Poland

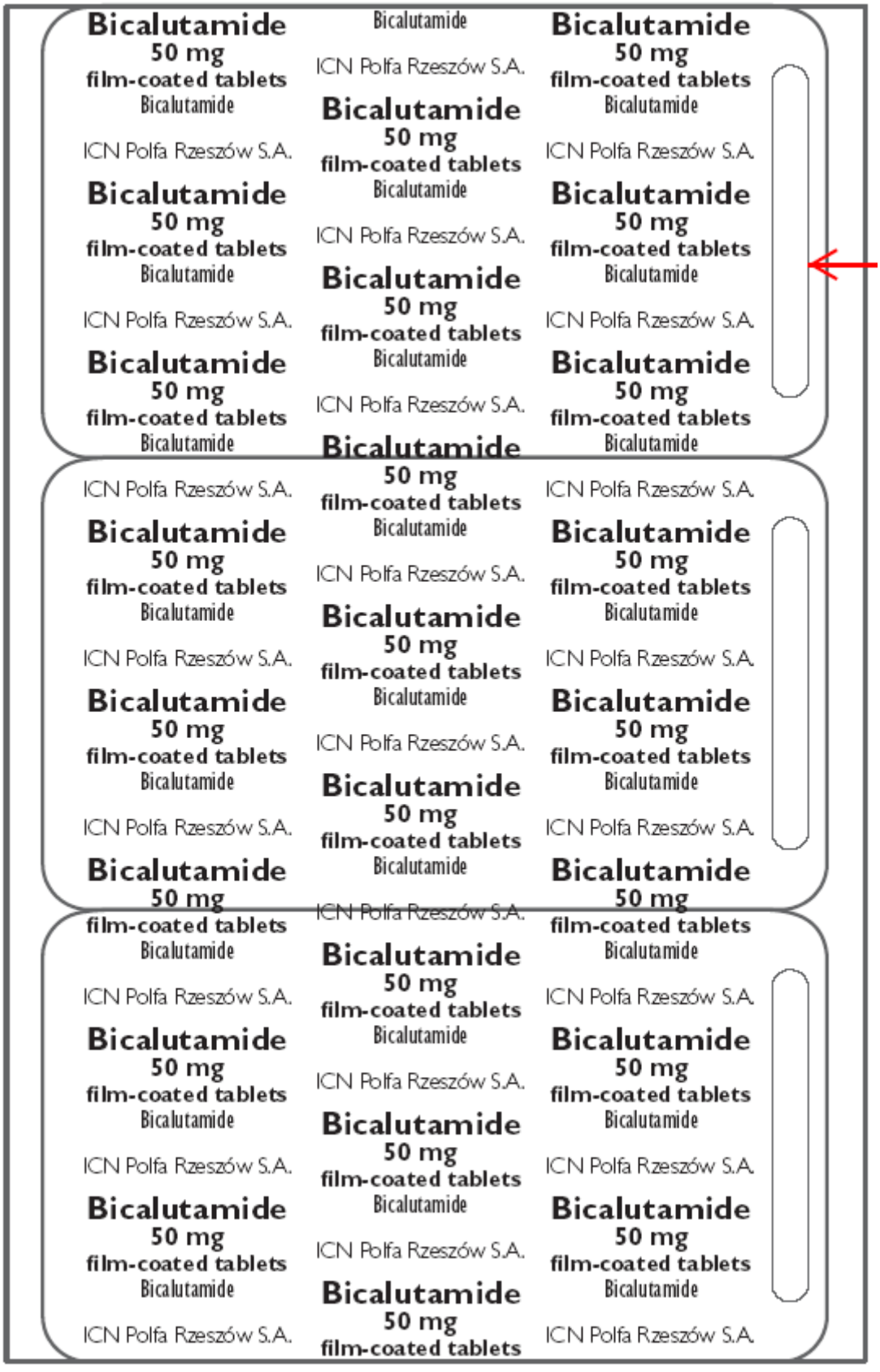
Manufacturer
ICN Polfa Rzeszów S.A.
2 Przemysłowa Street
35-959 Rzeszów
Poland
&
Genepharm S.A
18th klm Marathonos Avenue,
153 51 Pallini Attikis
Greece

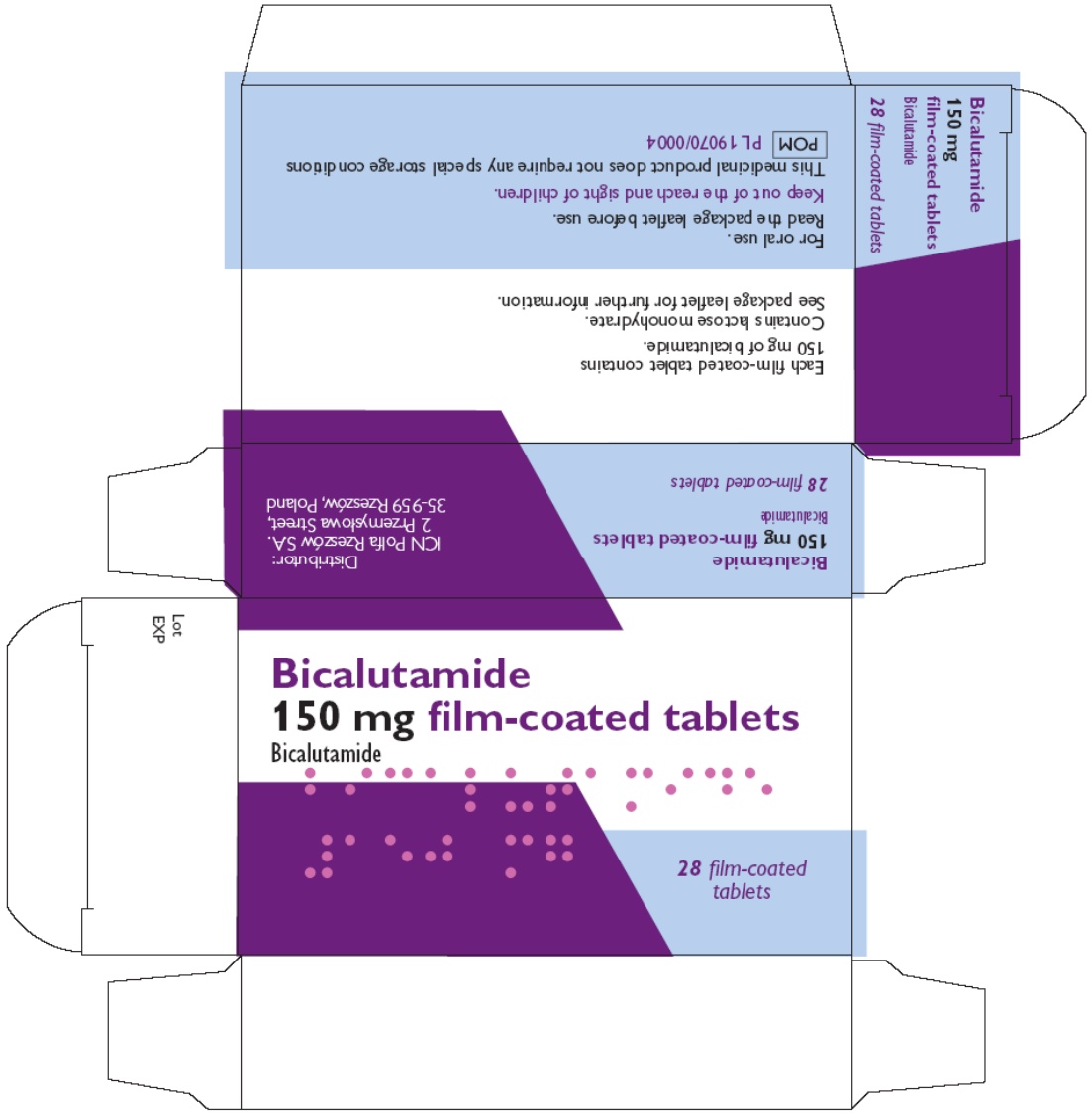
This medicinal product is authorised in the Member States of the EEA under the following names:
UK:
Bicalutamide, 150 mg, film-coated tablets
PL:
Prostide, 150 mg, tabletki powlekane
HU:
Grommar, 150 mg, filmtabletta
SK:
Glanuta, 150 mg, filmom obalené tablety
CZ:
Glanuta, 150 mg, potahované tablety

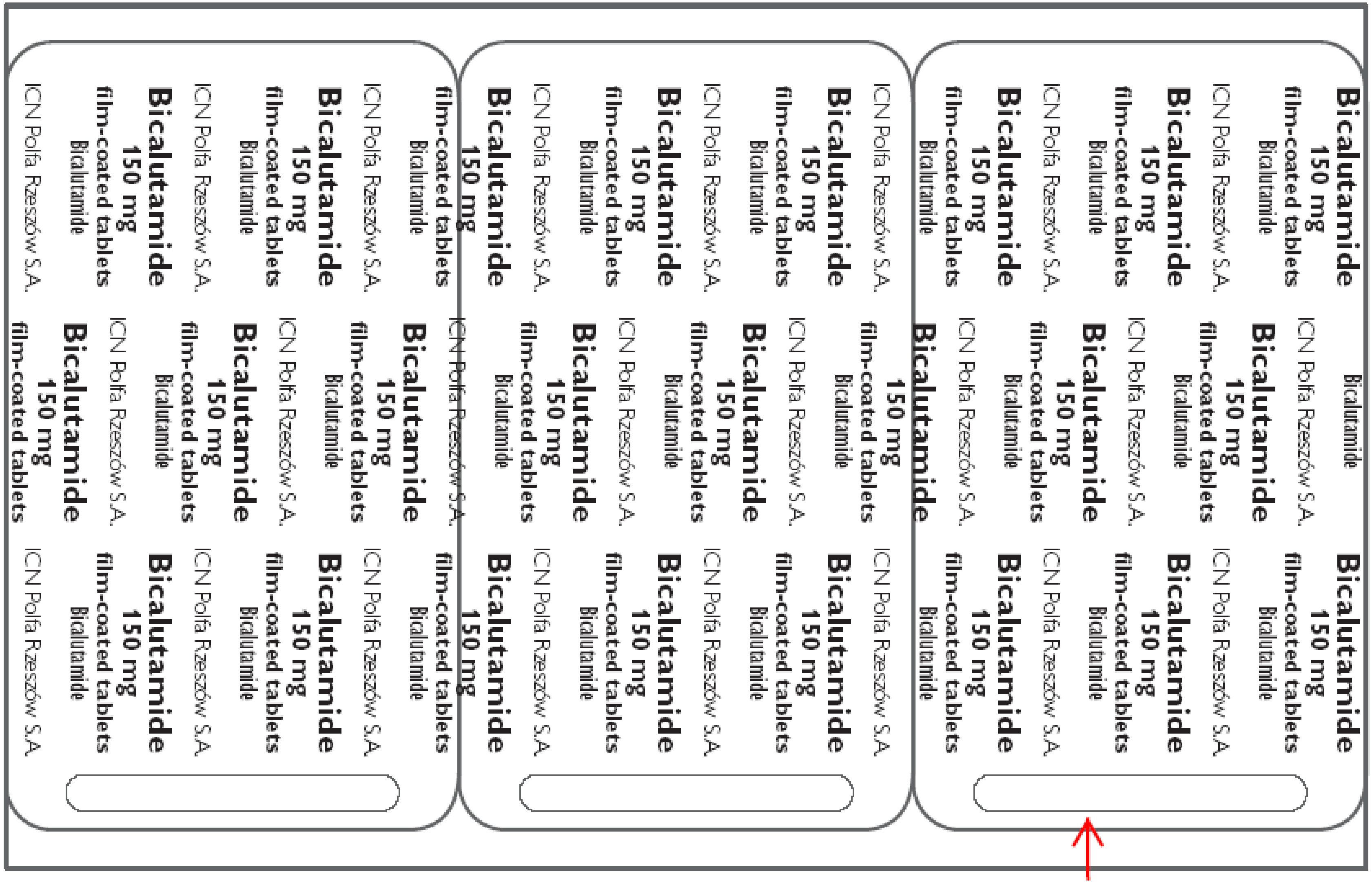
This leaflet was last approved in August 2008

Module 4
Labelling




Bicalutamide
50 mg
film-coated tablets
Bicalutamide
ICN Polfa Rzeszów S.A.


Bicalutamide
150 mg film-coated tablets
Bicalutamide
28 film-coated tablets
Each film-coated tablet contains
150 mg of bicalutamide.
Contains lactose monohydrate.
See package leaflet for further information.
For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions
POM
PL 19070/0004
Bicalutamide
150 mg film-coated tablets
Bicalutamide
28 film-coated tablets
Distributor:
ICN Polfa Rzeszów SA.
2 Przemysłowa Street,
35-959 Rzeszów, Poland
Lot
EXP
Bicalutamide
150 mg film-coated tablets
Bicalutamide
28 film-coated tablets


Bicalutamide
150 mg
film-coated tablets
Bicalutamide
ICN Polfa Rzeszów S.A.

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Czech Republic, Hungary, Poland, the Slovak Republic and the UK have granted marketing authorisations for Bicalutamide 50mg and 150mg Film-Coated Tablets to ICN Polfa Rzeszów S.A for the treatment of:

- 50mg - advanced prostate cancer in combination with luteinising hormone releasing hormone analogue therapy or surgical castration
- 150mg - either alone or as adjuvant to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer at high risk for disease progression.

These applications for Bicalutamide 50mg and 150mg Film-Coated Tablets are made using the decentralised procedure (DCP), under Article 10.1 of 2001/83 EC, claiming to be generic medicinal products to Casodex 50mg and 150mg Tablets (AstraZeneca UK Limited), authorised in the UK since the 23rd February 1995.

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.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product.

The applicant has provided an acceptable justification for not submitting a European Risk Management Plan. Other documentation relating to Pharmacovigilance System has been provided.

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 sites.

The decentralised procedure was concluded on 1st September 2008 (Day 210). A subsequent national licence was granted in the UK on 9th October 2008.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Bicalutamide 50mg Film-Coated Tablets Bicalutamide 150mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Bicalutamide
Pharmacotherapeutic classification (ATC code)	Non-steroidal anti-androgen (L02B B03)
Pharmaceutical form and strength(s)	Film-Coated Tablets 50and 150mg
Reference numbers for the Decentralised Procedure	UK/H/1270/001-2/DC
Reference Member State	United Kingdom
Member States concerned	Czech Republic, Hungary, Poland and Slovak Republic
Name and address of manufacturer responsible for batch release in the EEA	1. Genepharm SA, 18th Klm Marathos Avenue, 153 51 Pallini Attikis – Greece
	2. ICN Polfa Rzeszów S.A., 2 Przemysłowa Street, 35-959 Rzeszów – Poland
Marketing Authorisation Number(s)	PL 19070/0003-4
Name and address of the authorisation holder	ICN Polfa Rzeszów S.A., 2 Przemysłowa Street, 35-959 Rzeszów – Poland

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

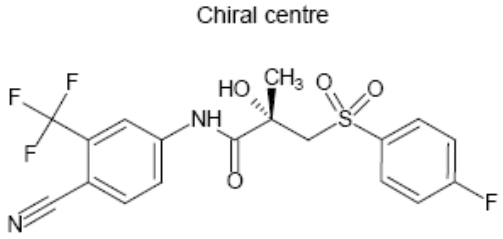
Active Substance

INN: Bicalutamide

Chemical Name: RS *N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl propanamide

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

Chemical Structure:



Molecular Weight: 430.38

Appearance: White to almost-white crystalline powder

Properties: Soluble in DMF and acetone, slightly soluble in methanol, practically insoluble in chloroform and water.

Chirality: The RS Bicalutamide is a racemic anti androgen. A mixture of R and S enantiomers are generally referred to as a racemic mixture. R enantiomer is primarily responsible for the anti-androgenic activity.

Polymorphism: Bicalutamide exists in two forms i.e. crystalline form-1 and crystalline form-2.

There is no European Pharmacopoeia monograph for bicalutamide.

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

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

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

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

Appropriate stability data have been generated supporting a retest period of 3 years when stored in the proposed containers.

Other Ingredients
Other ingredients consist of pharmaceutical excipients lactose monohydrate, povidone K-25, sodium starch glycolate Type A, magnesium stearate and a film coating (consisting of hypromellose 5cP (E464), titanium dioxide (E171) and propylene glycol).

All excipients comply with their respective European Pharmacopoeia monograph.

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

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

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

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

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

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

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

Container-Closure System
All strengths of tablet are packaged in aluminium/polyvinylchloride/polyvinylidene chloride blister strips, which are packed into cardboard cartons in pack sizes of 10, 28, 30 and 90 tablets. Not all pack sizes are to be marketed, however, the marketing authorisation holder has committed to submitting the proposed packaging/labelling for any pack size before it is marketed.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.

Stability of the product
Stability studies were performed on batches of all strengths of finished product in accordance with current guidelines. The results support a shelf-life of 30 months, with no specific storage conditions.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

The test products used in the bioequivalence studies comparing the 50 and 150mg strengths were manufactured using active bicalutamide from a different active substance manufacturer from the one proposed in the marketing authorisation application. However, certificates of analysis, process validation results, and dissolution results between the test batches used in the bioequivalence study and the 50/150mg strengths that are proposed for marketing show that they are comparable products.

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

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

Labelling
These are satisfactory

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

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

MAA Forms
These are satisfactory.

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

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

III.2 PRE-CLINICAL ASPECTS

These applications have been made under Article 10.1, claiming to be generic medicinal products to Casodex 50mg and 150mg Tablets (AstraZeneca UK Limited), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A pre-clinical expert report has been prepared by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

III.3 CLINICAL ASPECTS

III.3.1 Clinical Pharmacology

Apart from the bioequivalence studies, no new data were submitted and none are required for applications of this nature.

Bioequivalence Study - 50mg Strength Film-Coated Tablets

This was an open-label, crossover, randomised, two-period, two-treatment study comparing plasma pharmacokinetics of the test product, Bicalutamide 50mg Film-Coated Tablets, versus the reference product, Casodex 50mg Tablets (AstraZeneca GmbH, Germany), in healthy male volunteers.

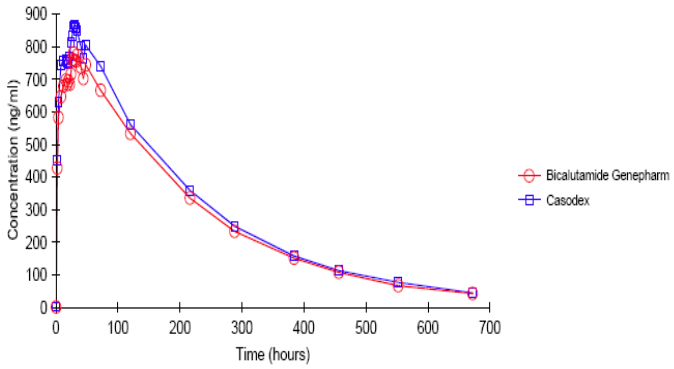
Blood samples were taken pre-dose and up to 672 hours post dose. The washout period was between 35 and 56 days. The relevant pharmacokinetic results from this study are presented below:

Treatment	AUC_{0-t} ng.hr/ml Mean (+/- SD) [Range]	$AUC_{0-\infty}$ ng.hr/ml Mean (+/- SD) [Range]	C_{max} ng/ml Mean (+/- SD) [Range]	T_{max} hr Mean (+/- SD) [Range]	$T_{1/2}$ hr Mean (+/- SD) [Range]
Test	181777.81 (+/- 45212.19) [104275.22-295731.58]	195653.04 (+/-56739.98) [56739.98-105374.85]	842.05 (+/- 119.59) [628.20-1028.00]	31.72 (+/- 10.16) [12.00-48.12]	145.90 (+/- 45.28) [87.43-261.46]
Reference	194783 (+/- 46572.97) [108710.69-29161.61]	210102.30 (+/- 61018.20) [112152.37-355297.5]	926.34 (+/- 157.10) [585.40-1179.00]	28.47 (+/- 8.56) [8.00-48.00]	146.74 (+/- 51.65) [84.61-320.58]
***Ratio (90% CI)**	89.64-96.58	88.99-97.11	87.66-95.22		

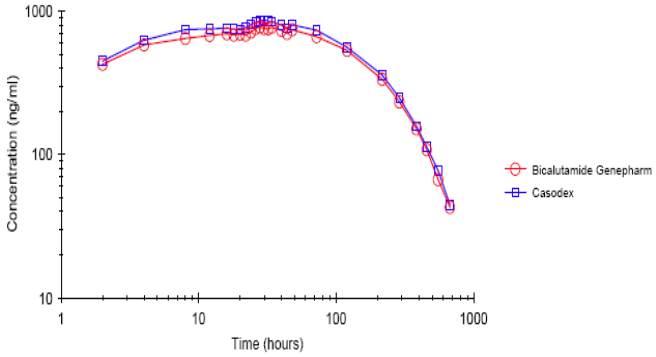
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration
$T_{1/2}$	half-life

**ln-transformed values*

Mean plasma concentration (ng/ml) versus time (hrs) for bicalutamide



Log transformed Mean plasma concentration (ng/ml) versus time (hrs) for bicalutamide



The 90% confidence intervals for AUC and C_{max} are within the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* limits. Thus, the test 50mg product can be considered as a generic medicinal product to the reference product, Casodex 50mg Tablets.

Bioequivalence Study - 150mg Strength Film-Coated Tablets

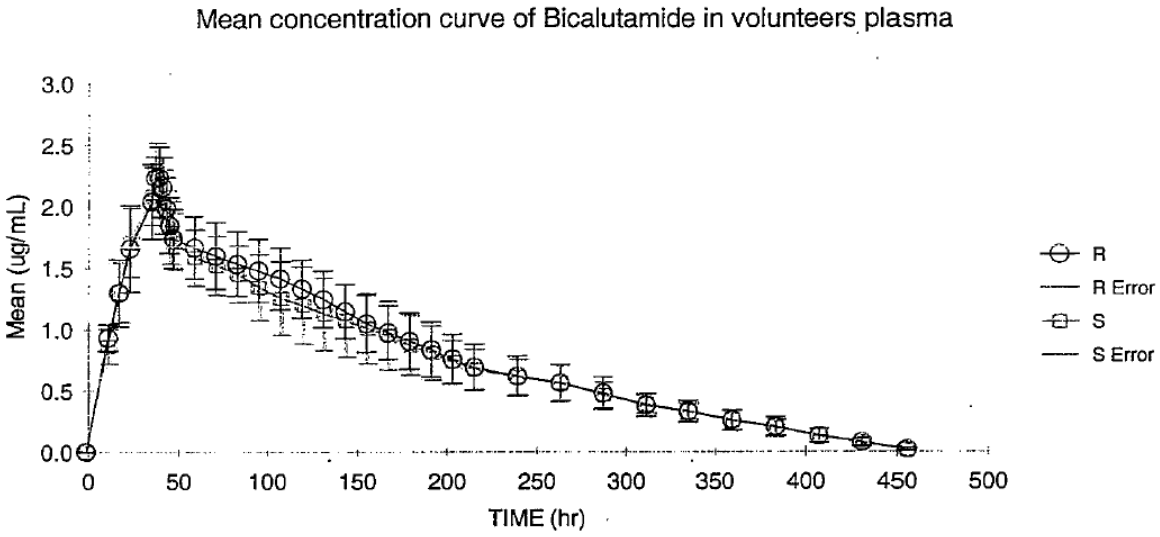
This was an open-label, crossover, randomised, two-period, two-treatment study comparing plasma pharmacokinetics of the test product, Bicalutamide 150mg Film-Coated Tablets, versus the reference product, Casodex 150mg Tablets (AstraZeneca SA, Greece), in healthy male volunteers.

Blood samples were taken pre-dose and up to 456 hours post dose. The washout period was between 4 weeks. The relevant pharmacokinetic results from this study are presented below:

Treatment	**AUC_{0-t}** ng.hr/ml Mean [Range]	**$AUC_{0-\infty}$** ng.hr/ml Mean [Range]	**C_{max}** ng/ml Mean [Range]	**T_{max}** hr Mean [Range]	**$T_{1/2}$** hr Mean [Range]
Test	337461 (228755-437315)	339637 (231334-438216)	2392 (2080-2757)	38.0 (36.0-42.0)	78.476 (60.485-109.084)
Reference	349582 (253248-482344)	351451 (253910-483323)	2381 (2161-2771)	38.0 (36.0-42.0)	73.492 (56.670-89.159)
***Ratio (90% CI)**	87.95-105.95	88.07-106.04	96.48-104.61		

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration
$T_{1/2}$	half-life

****ln-transformed values***



The 90% confidence intervals for AUC and C_{max} are within the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* limits. Thus, the test 150mg product can be considered as a generic medicinal product to the reference product, Casodex 150mg Tablets.

III.3.2 Clinical Efficacy
No new data.

III.3.3 Clinical Safety
In both bioequivalence studies, the treatments were well-tolerated. No deaths or serious adverse events occurred and the adverse event profiles were in-line with the prescribing information for the reference products.

Module 1 – Administrative information
MAA forms
The MAA forms are medically satisfactory.

Summary of Product Characteristics (SPC)
The SPCs are in-line with those for the reference products and are medically satisfactory.

Patient Information Leaflet (PIL)
The PIL is in-line with that for the reference products and is medically satisfactory.

Packaging
The packaging is medically satisfactory.

Module 2 – Clinical overall summary
A clinical overall summary, written by an appropriately qualified physician and is a satisfactory summary of the clinical aspects of the dossier.

Conclusions on safety
The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

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

Bioequivalence has been demonstrated between the applicant's 50 and 150mg tablets and the reference products Casodex 50mg and 150mg Tablets.

No new or unexpected safety concerns arise from these applications.

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

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

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome