Safeguarding public health

MHRA

Public Assessment Report

Bicasel 50mg Film-coated Tablets (bicalutamide)

PL 19053/0034

Bicamale 50mg Film-coated Tablets (bicalutamide)

PL 19053/0036

Medicines and Healthcare products Regulatory Agency

BICASEL 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0034

BICAMALE 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0036

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BICASEL 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0034

BICAMALE 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0036

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Tenlec Pharma Limited Marketing Authorisations (licences) for the medicinal products Bicasel 50mg Film-coated Tablets (PL 19053/0034) and Bicamale 50mg Film-coated Tablets (PL 19053/0036). These are prescription only medicines [POMs] used to treat prostate cancer.

These products contain the active substance bicalutamide. Bicalutamide belongs to a group of medicines called antiandrogens. It interferes with some of the actions of the male sex hormones.

The clinical data presented to the MHRA, before licensing, demonstrated that Bicasel/Bicamale 50mg Film-coated Tablets are essentially similar or equivalent to the approved product, Casodex 50mg Tablets, and as such can be used interchangeably.

No new or unexpected safety concerns arose from these applications and it was decided that the benefits of using Bicasel/Bicamale 50mg Film-coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.

BICASEL 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0034

BICAMALE 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0036

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Bicasel 50mg Film-coated Tablets (PL 19053/0034) and Bicamale 50mg Film-coated Tablets (PL 19053/0036) to Tenlec Pharma Limited on 15 September 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Casodex 50mg Tablets.

These products contain the active ingredient bicalutamide and are indicated for the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

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.

PHARMACEUTICAL ASSESSMENT

PL Numbers:	**PL 19053/0034** **PL 19053/0036**
Product:	**Bicasel 50mg Film-coated Tablets** **Bicamale 50mg Film-coated Tablets**
Marketing Authorisation Holder:	**Tenlec Pharma Limited**
Active ingredient(s):	**Bicalutamide**
EC Article:	**10.1(a)(iii)**
Legal Status:	**POM**

INTRODUCTION

These are abridged applications for Marketing Authorisations in the UK submitted under Article 10.1(a)(iii) of Directive 2001/83/EC as amended, for a product claiming essential similarity to Casodex 50mg Tablets, initially PL 12619/0102 (granted 23 February 1995) but which has undergone a change of ownership and is now marketed on licence PL 17901/0005, granted to AstraZeneca UK Limited.

DRUG SUBSTANCE

The drug substance is the subject of a drug substance master file (DMF) which has been assessed and is acceptable. A letter of access to the DMF is provided.

Control of drug substance

Specification

There is currently no pharmacopoeial monograph for this active substance so an in-house specification is proposed to control the quality of the active. This is acceptable.

DRUG PRODUCT

Description and composition of the drug product

The tablets are presented as white, round, biconvex and film-coated.

Composition of tablets

Constituent	Reference Standards	Function
Active		
Bicalutamide	In-house	Active substance
Tablet core		
Lactose monohydrate	Ph.Eur.	Filler
Povidone K-30	Ph.Eur.	Binder
Sodium starch glycolate	Ph.Eur.	Disintegrant
Magnesium Stearate	Ph.Eur.	Lubricant
Film-coating		
Opadry White Y-1-7000	In-house	Taste-masking/film binder

Excipients of coating material Opadry White Y-1-7000

Constituent	Reference Standard
Hypromellose	Ph.Eur.
Titanium dioxide	Ph.Eur.
Macrogol 400	Ph.Eur.

Type of container and closure of the dosage form

The primary packaging material is blisters of Al/PVC foil and Al/PVC/PVDC foil.

Pharmaceutical development

Satisfactory development data has been provided.

Manufacture

Manufacturer

The manufacturing site is suitable and a satisfactory statement from the competent authority has been provided.

The batch release site is Helm Pharmaceuticals GmbH, Hamburg, Germany.

Batch formula

The batch formula for the routine manufacturing batch has been provided.

Description of manufacturing process and process controls

A flow diagram outlining the various stages of the manufacturing process and the in-process controls is provided. A narrative description and process parameters are also presented.

Control of critical steps and intermediates

Satisfactory details provided.

Process validation and/or Evaluation

Satisfactory data provided.

Control of excipients

Specifications

All the excipients except the coating agent have a Ph.Eur. monograph, and are tested according to Ph.Eur. methods. Copies of Certificates of Analysis (COAs) for the excipients have been provided.

Magnesium stearate is prepared from vegetable sources.

The Opadry White Y-1-7000 coating agent is controlled to an in-house specification. COAs are supplied by the applicant and by the manufacturer**.**

Control of Drug Product

Specification

The tablets are tested to a suitable specification.

Analytical procedures
Validation of analytical procedures

Where feasible, the test methods of the Ph.Eur. are employed. Suitable and validated in-house methods were also used.

Batch analyses

Certificates of Analysis have been presented for three batches. These are the validation batches. There is little inter-batch variation.

Container closure system

The specifications for PVC foil, PVC/PVDC foil and aluminium foil have been supplied and relate to dimensions and weights. The packaging materials all comply with EC Directive 90/128, as amended, for materials in direct contact with foodstuff.

Stability

Real time (25°C±2^{0}C/60%±5%RH), intermediate (30°C±2^{0}C/65%±5%RH) and accelerated (40°C±2^{0}C/75%±5%RH) stability studies have been conducted. These support the proposed shelf life of 18 months with no special storage conditions.

The applicant has provided a protocol for stability studies post approval.

BIOEQUIVALENCE / BIOAVAILABILITY

Bioequivalence of bicalutamide was investigated in a single centre using a single dose, randomized, 2-way crossover study on the 50mg strength.

The applicant's bicalutamide 50mg Tablets was compared with Casodex 50mg Tablets. The tested tablets were administered as 1 X 50mg dose to 30 healthy male volunteers under fasting conditions. The treatment phases were separated by a washout period of 42 days.

Thirty individuals were screened for the study, of which the first 24 who completed all the treatment periods were included in the pharmacokinetic analyses

In accordance with the study protocol, the hypothesis of bioequivalence of the formulations was accepted if the 90% geometric confidence intervals of least-squares means ratios of the test to reference products of ln-transformed AUC_{0-t} and C_{max} were within the acceptance range of 80% to 125%. The point estimated for AUC_{0-t} is 97.03%, AUC_{0-inf} is 97.43% and C_{max} is 98.08%. This study meets the acceptance criteria (test vs reference: 92.68% to 101.58% for AUC_{0-t} and 95.70% to 100.52% for C_{max}). The C_{max} is within the linear range as validated.

A Certificate of Analysis for the reference product has been provided.

SUMMARY OF PRODUCT CHARACTERISTICS
PATIENT INFORMATION LEAFLET (PIL)
LABELLING

Satisfactory.

COMMENT ON THE QUALITY OVERALL SUMMARY

The summary provides a fairly comprehensive review of Module 3.

CONCLUSIONS AND ADVICE

The pharmaceutical development has been described and validation of the manufacturing method has been performed. Essential similarity of the generic product with the UK innovator product has been confirmed. These tablets can be granted Marketing Authorisations.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required.

CLINICAL ASSESSMENT

PL Numbers :	**PL 19053/0034**
	PL 19053/0036
Product:	**Bicasel 50mg Film-coated Tablets**
	Bicamale 50mg Film-coated Tablets
Marketing Authorisation Holder:	**Tenlec Pharma Limited**
Active ingredient(s):	**Bicalutamide**
EC Article:	**National**
Legal Status:	**POM**

INTRODUCTION

These are national generic applications for UK marketing authorisations.

Claiming essential similarity to the innovator product, the applicant has submitted applications for two generic products. Details of the reference medicinal product in the UK are as follows:

Product name:	Casodex 50mg Tablets
MA:	17901/0005
MA holder:	AstraZeneca UK Limited

Bicalutamide is a non-steroidal anti-androgen, devoid of other endocrine activity. It binds to androgen receptors without activating gene expression, and thus inhibits the androgen stimulus. The drug is a racemate with its antiandrogenic activity being almost exclusively in the(R)-enantiomer. Bicasel/Bicamale 50mg Tablets are indicated for "treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration."

SUMMARIES OF PRODUCT CHARACTERISTICS

The Summaries of Product Characteristics of the generic products under assessment and the Summary of Product Characteristics for the reference product from the innovator in the UK are identical with respect to Sections 4 and 5. In addition, the SPCs under assessment include a warning related to the lactose content of the tablets (Section 4.4) and ATC coding (Section 5.1).

BIOEQUIVALENCE STUDY

Study design

Open randomised two-way crossover, single dose study under fasting conditions

Enrolled and randomised:	n = 30
Drop outs:	n = 0
Withdrawals:	n = 0
Completed:	n =30

30 healthy volunteers for safety (received at least one treatment)
24 healthy volunteers for pharmacokinetics (completed both treatment periods)

Sampling to 672 hours
Washout period 42 days

Results

Pharmacokinetic dataset

N = 24 (subject numbers 1 to 25 but excluding number 18)

The applicant has argued that subject attrition was expected due to the long washout period of the study. For this reason, 6 subjects more than required for bioequivalence were included. As per study protocol, the first 24 subjects to complete the study had their plasma samples analysed and were used in pharmacokinetic and statistical analyses. Subject No. 18 was not used in the pharmacokinetic analysis because of the use of concomitant medication.

	Test product (T)			Reference product (R)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
C_{max} (ng/ml)	693.03	99.74	14.39	707.85	91.26	12.89
Tmax (h)	25.6	12.1	47.10	29.6	11.1	37.35
$AUC_{(0-t)}$ (ng.h/ml)	143277.90	28102.89	19.61	148760.20	32638.62	21.94
$AUC_{(0-\alpha)}$ (ng.h/ml)	148820.22	30695.39	20.63	154126.51	36776.37	23.86
$\frac{AUC(0-t)}{AUC(0-\alpha)}$	96.3%			96.5%		
$t_{1/2}$ (h)	118.07	35.00	29.64	117.53	34.89	29.69
K_{el} (h^{-1})	0.0063	0.0016	25.85	0.0064	0.0017	26.48

	Ratio of least square means of T / R	90% Geometric CI	Intrasubject CV (%)
Cmax (ng/ml)	98.08 %	95.70– 100.52	4.94
AUC(0-t) (ng.h/ml)	97.03 %	92.68 – 101.58	9.23
AUC(0-α) (ng.h/ml)	97.43 %	93.14 – 101.91	9.06

No statistically significant differences between the test and reference products were detected using ANOVA for ln-transformed C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\alpha)}$ as well as for untransformed K_{el} and $t_{1/2}$.

ANOVA detected a statistically significant period effect for C_{max}. This could be an indication of an equal carry over effect. Since there was no sequence effect, it is concluded that there was no indication of an unequal carryover effect. No statistically significant differences were detected between treatments for T_{max}.

There were 31 adverse events:

- 3 were clinically significant laboratory abnormalities which could not be assigned to any one treatment.
  Subject 06: Haemoglobin 12.6 g/100ml. Repeat test normal
  Subject 18: Proteinuria of 1.00 g/L. Repeat still positive (30g/L).
  Subject 23: ALT of 76 U/L. Repeat test normal.

- There were 7 events related to treatment A (test) and 21 to treatment B (reference).

Conclusion

By the criteria usually applied, the two 50mg products appear to be bioequivalent.

PATIENT INFORMATION LEAFLET

Satisfactory.

RECOMMENDATIONS

There are no issues relating to the Summaries of Product Characteristics.

The recommendation is to grant marketing authorisations for these preparations.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Bicasel/Bicamale 50mg 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.

PRECLINICAL

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

EFFICACY

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

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of Casodex 50mg Tablets.

RISK-BENEFIT ASSESSMENT

The quality of the products 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 innovator product are interchangeable. The risk-benefit assessment is therefore considered to be favourable.

BICASEL 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0034

BICAMALE 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0036

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications for Bicasel/Bicamale 50mg Film-coated Tablets on 15 April 2005.
2	The MHRA's assessment of the submitted quality data was completed on 21 September 2005.
3	Further information (quality) was requested from the company on 8 November 2005.
4	The MHRA's assessment of the submitted clinical data was completed on 8 January 2006.
5	Further information (clinical) was requested from the company on 8 January 2006.
6	The applicant's response to further information request (clinical) was sent in a letter dated 12 April 2006.
7	The applicant's response to further information request (quality) was sent in a letter dated 18 May 2006.
8	The MHRA completed its assessment of the applications on 14 September 2006.
9	The applications were determined on 15 September 2006.

BICASEL 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0034

BICAMALE 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0036

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bicasel 50mg Film-coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg bicalutamide

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
White, round, biconvex film-coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Adult males including the elderly: one tablet (50mg) once a day.
Treatment with Bicasel should be started at least 3 days before commencing treatment with an LHRH analogue, or at the same time as surgical castration.

Children: Bicasel is contraindicated in children.

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

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

4.3 Contraindications

Bicasel is contraindicated in females and children.

Bicasel must not be given to any patient who has shown a hypersensitivity reaction to bicalutamide or to any of the excipients.
Co-administration of terfenadine, astemizole or cisapride with Bicasel is contraindicated.

4.4 Special warnings and precautions for use

Bicalutamide is extensively metabolised in the liver. Data suggests that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide. Therefore, Bicasel should be used with caution in patients with moderate to severe hepatic impairment.
Periodic liver function testing should be considered due to the possibility of hepatic changes. The majority of changes are expected to occur within the first 6 months of Bicasel therapy.
Severe hepatic changes have been observed rarely with bicalutamide (see Section 4.8). Bicasel therapy should be discontinued if changes are severe.

Bicalutamide has been shown to inhibit Cytochrome P450 (CYP 3A4), as such, caution should be exercised when co-administered with drugs metabolised predominantly by CYP 3A4, see Sections 4.3 and 4.5.

Bicasel contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Bicasel.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide and LHRH analogues.

In vitro studies have shown that R-bicalutamide is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.
Although clinical studies using antipyrine as a marker of cytochrome P450 (CYP) activity showed no evidence of a drug interaction potential with bicalutamide, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of bicalutamide for 28 days. For drugs with a narrow therapeutic index such an increase could be of relevance. As such, concomitant use of terfenadine, astemizole and cisapride is contraindicated and caution should be exercised with the co-administration of Bicasel 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 Bicasel therapy.

Caution should be exercised when prescribing Bicasel with other drugs which may inhibit drug oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of bicalutamide which theoretically could lead to an increase in side effects.

In vitro studies have shown that bicalutamide can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is therefore recommended that if Bicasel is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

4.6 Pregnancy and lactation

Bicasel is contraindicated in females and must not be given to pregnant women or nursing mothers.

4.7 Effects on ability to drive and use machines

Bicasel is unlikely to impair the ability of patients to drive or operate machinery. However, it should be noted that occasionally somnolence may occur. Any affected patients should exercise caution.

4.8 Undesirable effects

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

Table 1: Frequency of Adverse Reactions

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

1. May be reduced by concomitant castration.

2. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4).

3. Hepatic failure has occurred very rarely in patients treated with bicalutamide, but a causal relationship has not been established with certainty. Periodic liver function testing should be considered (see also section 4.4).

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

Thrombocytopenia has been reported rarely.

In addition, the following adverse experiences were reported in clinical trials (as possible adverse drug reactions in the opinion of investigating clinicians, with a frequency of 1%) during treatment with bicalutamide plus an LHRH analogue. No causal relationship of these experiences to drug treatment has been made and some of the experiences reported are those that commonly occur in elderly patients:
Cardiovascular system: heart failure.
Gastrointestinal system: anorexia, dry mouth, dyspepsia, constipation, flatulence.
Central nervous system: dizziness, insomnia, somnolence, decreased libido.
Respiratory system: dyspnoea.
Urogenital: impotence, nocturia.
Haematological: anaemia.
Skin and appendages: alopecia, rash, sweating, hirsutism.
Metabolic and nutritional: diabetes mellitus, hyperglycaemia, oedema, weight gain, weight loss.
Whole body: abdominal pain, chest pain, headache, pain, pelvic pain, chills.

4.9 Overdose

There is no human experience of overdose. 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

ATC code: L02B B03
Pharmacotherapeutic group: Non-steroidal antiandrogen

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.
On daily administration of bicalutamide, the (R)-enantiomer accumulates about 10 fold in plasma as a consequence of its long half-life.
Steady state plasma concentrations of the (R)-enantiomer of approximately 9 microgram/ml are observed during daily administration of 50 mg doses of bicalutamide. At steady state the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.
The pharmacokinetics of the (R)-enantiomer are unaffected by age, renal impairment or mild to moderate hepatic impairment. There is evidence that for subjects with severe hepatic impairment, the (R)-enantiomer is more slowly eliminated from plasma.
Bicalutamide is highly protein bound (racemate 96%, R-bicalutamide 99.6%) and extensively metabolised (via oxidation and glucuronidation): Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Povidone K-30
Sodium starch glycolate
Magnesium stearate
Film-coating:
Opadry WhiteY-1-7000 consisting of –
Hypromellose
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

There are no special conditions for storage.

6.5 Nature and contents of container

Aluminium/PVC foil or Aluminium/PVC/PVDC foil blisters in an outer cardboard carton containing 10, 14, 28, 30, 50, 60, 90 or 100 film-coated tablets

6.6 Special precautions for disposal

No special precautions required.

7 MARKETING AUTHORISATION HOLDER

Tenlec Pharma Ltd
Broadlands
Amberstone
Hailsham
East Sussex BN27 1PQ

8 MARKETING AUTHORISATION NUMBER(S)

PL 19053/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/09/2006

10 DATE OF REVISION OF THE TEXT

15/09/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bicamale 50mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg bicalutamide

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
White, round, biconvex film-coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Adult males including the elderly: one tablet (50mg) once a day.
Treatment with Bicamale should be started at least 3 days before commencing treatment with an LHRH analogue, or at the same time as surgical castration.

Children: Bicamale is contraindicated in children.

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

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

4.3 Contraindications

Bicamale is contraindicated in females and children.
Bicamale must not be given to any patient who has shown a hypersensitivity reaction to bicalutamide or to any of the excipients.

Co-administration of terfenadine, astemizole or cisapride with Bicamale is contraindicated.

4.4 Special warnings and precautions for use

Bicalutamide is extensively metabolised in the liver. Data suggests that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide. Therefore, Bicamale should be used with caution in patients with moderate to severe hepatic impairment.
Periodic liver function testing should be considered due to the possibility of hepatic changes. The majority of changes are expected to occur within the first 6 months of Bicamale therapy.
Severe hepatic changes have been observed rarely with bicalutamide (see Section 4.8). Bicamale therapy should be discontinued if changes are severe.

Bicalutamide has been shown to inhibit Cytochrome P450 (CYP 3A4), as such, caution should be exercised when co-administered with drugs metabolised predominantly by CYP 3A4, see Sections 4.3 and 4.5.

Bicamale contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Bicamale.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide and LHRH analogues.

In vitro studies have shown that R-bicalutamide is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.
Although clinical studies using antipyrine as a marker of cytochrome P450 (CYP) activity showed no evidence of a drug interaction potential with bicalutamide, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of bicalutamide for 28 days. For drugs with a narrow therapeutic index such an increase could be of relevance. As such, concomitant use of terfenadine, astemizole and cisapride is contraindicated and caution should be exercised with the co-administration of Bicamale 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 Bicamale therapy.

Caution should be exercised when prescribing Bicamale with other drugs which may inhibit drug oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of bicalutamide which theoretically could lead to an increase in side effects.

In vitro studies have shown that bicalutamide can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is therefore recommended that if Bicamale is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

4.6 Pregnancy and lactation

Bicamale is contraindicated in females and must not be given to pregnant women or nursing mothers.

4.7 Effects on ability to drive and use machines

Bicamale is unlikely to impair the ability of patients to drive or operate machinery. However, it should be noted that occasionally somnolence may occur. Any affected patients should exercise caution.

4.8 Undesirable effects

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

Table 1: Frequency of Adverse Reactions

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	General disorders	Hot flushes[1]
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	Hepato-biliary disorders	Hepatic changes (elevated levels of transaminases, cholestasis and jaundice)[2]
	General disorders	Asthenia Pruritus
Uncommon ≥0.1% and <1%)	Immune system disorders	Hypersensitivity reactions, including angioneurotic oedema and urticaria
	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease
Rare ≥0.01% and < 0.1%)	Gastrointestinal disorders	Vomiting
	Skin and subcutaneous tissue disorders Hepato-biliary disorders	Dry skin Hepatic failure[3]

4. May be reduced by concomitant castration.

5. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4).

6. Hepatic failure has occurred very rarely in patients treated with bicalutamide, but a causal relationship has not been established with certainty. Periodic liver function testing should be considered (see also section 4.4).

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

Thrombocytopenia has been reported rarely.

In addition, the following adverse experiences were reported in clinical trials (as possible adverse drug reactions in the opinion of investigating clinicians, with a frequency of 1%) during treatment with bicalutamide plus an LHRH analogue. No causal relationship of these experiences to drug treatment has been made and some of the experiences reported are those that commonly occur in elderly patients:
Cardiovascular system: heart failure.
Gastrointestinal system: anorexia, dry mouth, dyspepsia, constipation, flatulence.
Central nervous system: dizziness, insomnia, somnolence, decreased libido.
Respiratory system: dyspnoea.
Urogenital: impotence, nocturia.
Haematological: anaemia.
Skin and appendages: alopecia, rash, sweating, hirsutism.
Metabolic and nutritional: diabetes mellitus, hyperglycaemia, oedema, weight gain, weight loss.
Whole body: abdominal pain, chest pain, headache, pain, pelvic pain, chills.

4.9 Overdose

There is no human experience of overdose. 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

ATC code: L02B B03
Pharmacotherapeutic group: Non-steroidal antiandrogen

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.
On daily administration of bicalutamide, the (R)-enantiomer accumulates about 10 fold in plasma as a consequence of its long half-life.
Steady state plasma concentrations of the (R)-enantiomer of approximately 9 microgram/ml are observed during daily administration of 50 mg doses of bicalutamide. At steady state the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.
The pharmacokinetics of the (R)-enantiomer are unaffected by age, renal impairment or mild to moderate hepatic impairment. There is evidence that for subjects with severe hepatic impairment, the (R)-enantiomer is more slowly eliminated from plasma.
Bicalutamide is highly protein bound (racemate 96%, R-bicalutamide 99.6%) and extensively metabolised (via oxidation and glucuronidation): Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Povidone K-30
Sodium starch glycolate
Magnesium stearate
Film-coating:
Opadry WhiteY-1-7000 consisting of –
Hypromellose
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

There are no special conditions for storage.

6.5 Nature and contents of container

Aluminium/PVC foil or Aluminium PVC/PVDC foil blisters in an outer cardboard carton containing 10, 14, 28, 30, 50, 60, 90 or 100 film-coated tablets

6.6 Special precautions for disposal

No special precautions required.

7 MARKETING AUTHORISATION HOLDER

Tenlec Pharma Ltd
Broadlands
Amberstone
Hailsham
East Sussex BN27 1PQ

8 MARKETING AUTHORISATION NUMBER(S)

PL 19053/0036

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/09/2006

10 DATE OF REVISION OF THE TEXT

15/09/2006

Patient Information Leaflet

BICASEL 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0034

TENLEC PHARMA LTD

Patient Information Leaflet:

BICASEL 50MG FILM-COATED TABLETS
(Bicalutamide)

Read all of this leaflet carefully before you start taking/using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Bicasel 50mg is and what it is used for
2. Before you take/use Bicasel 50mg
3. How to take/use Bicasel 50mg
4. Possible side effects
5. Storing Bicasel 50mg

The Name of this medicine is Bicasel 50mg Film-coated tablets, referred to as Bicasel 50mg throughout this leaflet.
The active ingredient is 50mg bicalutamide.
Other ingredients are lactose monohydrate, povidone K30, sodium starch glycolate, and magnesium stearate. The tablets are coated with Opadry White Y-1-7000 which contains hypromellose, macrogol 400 and titanium dioxide (E171).

Marketing Authorisation Holder:
Tenlec Pharma Ltd, Broadlands, Amberstone, Hailsham, East Sussex BN27 1PQ

Manufacturer:
This medicine is manufactured by Helm Pharmaceuticals GmbH, Nordkanalstrasse 28, 20097 Hamburg, Germany.

1. What Bicasel 50mg is and what it is used for
Each film-coated tablet contains 50mg of the active ingredient bicalutamide.
Each pack contains 10, 14, 28, 30, 50, 60, 90 or 100 tablets.
Bicalutamide is one of a group of medicines called antiandrogens. It interferes with some of the actions of the male sex hormones. Bicasel 50mg is used to treat prostate cancer.

2. Before you take/use Bicasel 50mg

Bicasel 50mg should NOT be used:
- By women, including pregnant women and those who are breast feeding their babies.
- By children
- If you have ever had an allergic reaction to bicalutamide or to any of the other ingredients.
- If you are taking anti-histamines called terfenadine or astemizole (used to treat rash and hay fever) or cisapride (used for some types of indigestion).

Before taking Bicasel 50mg, tell your doctor if:

- You are suffering from any condition which affects your liver
- You have been told by your doctor that you have an intolerance to some sugars
- You are taking other medicines. In particular, oral anti-coagulants (used to thin the blood), cyclosporin (used to suppress the immune system), calcium channel blockers (used to treat high blood pressure or some heart conditions), cimetidine (used to treat ulcers), midazolam (used as a tranquilliser) or ketoconazole (used to treat fungal infections)

Tell your doctor if you are taking any other medicine including those that you have bought.

Consult your doctor or pharmacist if these statements were applicable to you at any time in the past.

Pregnancy and breast feeding
Women must not take Bicasel 50mg.

Driving and using machines
Bicasel 50mg is unlikely to affect your ability to drive or operate machinery. However, if you feel drowsy while taking Bicasel 50mg you must exercise caution when carrying out these tasks.

Important information about some of the ingredients of Bicasel 50mg
Bicasel 50mg tablets contain lactose monohydrate. If you have an intolerance to some sugars you should tell your doctor before taking this medicine.

3. How to take/use Bicasel 50mg

Your doctor will have decided the right dose of Bicasel 50mg for you so follow his or her instructions.

The usual dose of Bicasel 50mg is one tablet daily.
Swallow the tablet whole with a drink of water. Try to take the tablet at the same time each day.

If you have the impression that the effect of Bicasel 50mg is too strong or too weak, talk to your doctor or pharmacist.

What if I miss a dose?
If you forget to take your medicine, take your dose when you remember then take your next dose at the usual time. Don't take two doses at the same time. If you are worried, ask your doctor or pharmacist for advice

What to do in case of an overdose
If you take more than your usual dose, contact your doctor. In the case of an overdose, contact the nearest hospital immediately and do not forget to take the carton with you to enable the doctors to know what has been taken.

Do not stop taking your tablets, even if you are feeling well, unless your doctor tells you.

REMEMBER –this medicine has been prescribed for you. Never give it to anyone else even if they have the same symptoms as it may harm them.

4. Possible side effects

Like all medicines, Bicasel 50mg may cause side effects.

If any of the following happen, stop taking Bicasel 50mg and tell your doctor immediately or go to the casualty department of the nearest hospital:
- Severe itching of the skin, swelling of the hands, feet, ankles, face, lips, mouth or throat which may cause difficulties in swallowing or breathing. You may have had a serious allergic reaction to Bicasel 50mg.
- Serious breathlessness, or sudden worsening of breathlessness, possibly with a cough or fever. You may have an inflammation of the lungs called interstitial lung disease.

All of these are serious side effects and are uncommon.

Tell your doctor if you notice any of the following:
Side effects that are very common:
- Tender or enlarged breasts
- Hot flushes

Side effects that are common:
- Diarrhoea
- Nausea
- Liver problems, yellowing of the skin or eyes (jaundice)
- Itching
- Feeling weak
- Development of breasts in males

Side effects that are rare:
- Vomiting
- Dry skin
- Liver problems
- Chest pains or palpitations

Occasionally Bicasel 50mg may cause changes in your blood, which require your doctor to do certain blood tests.

If you do experience side effects these usually disappear after a few days of treatment. If they are troublesome or persistent, or if you have side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. Storing Bicasel 50mg

Store in the original package. Keep out of the reach and sight of children.

Use by date: Do not use Bicasel 50mg after the expiry/use before date on the carton.

Further Information:
This leaflet does not include all the information about this medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.
If you have any medicine left over at the end of your treatment, please return this to your pharmacy who will dispose of it safely.

Date of preparation of the leaflet:
February 2006

BICAMALE 50MG FILM-COATED TABLETS
(BICALUTAMIDE)
PL 19053/0036

TENLEC PHARMA LTDL

Patient Information Leaflet:

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In this leaflet:
1. What Bicamale 50mg is and what it is used for
2. Before you take/use Bicamale 50mg
3. How to take/use Bicamale 50mg
4. Possible side effects
5. Storing Bicamale 50mg

The Name of this medicine is Bicamale 50mg Film-coated tablets referred to as Bicamale 50mg throughout this leaflet.
The active ingredient is 50mg bicalutamide.
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• You are taking other medicines. In particular, oral anti-coagulants (used to thin the blood), ciclosporin (used to suppress the immune system), calcium channel blockers (used to treat high blood pressure or some heart conditions), cimetidine (used to treat ulcers), midazolam (used as a tranquilliser) or ketoconazole (used to treat fungal infections)

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Labels/Packaging

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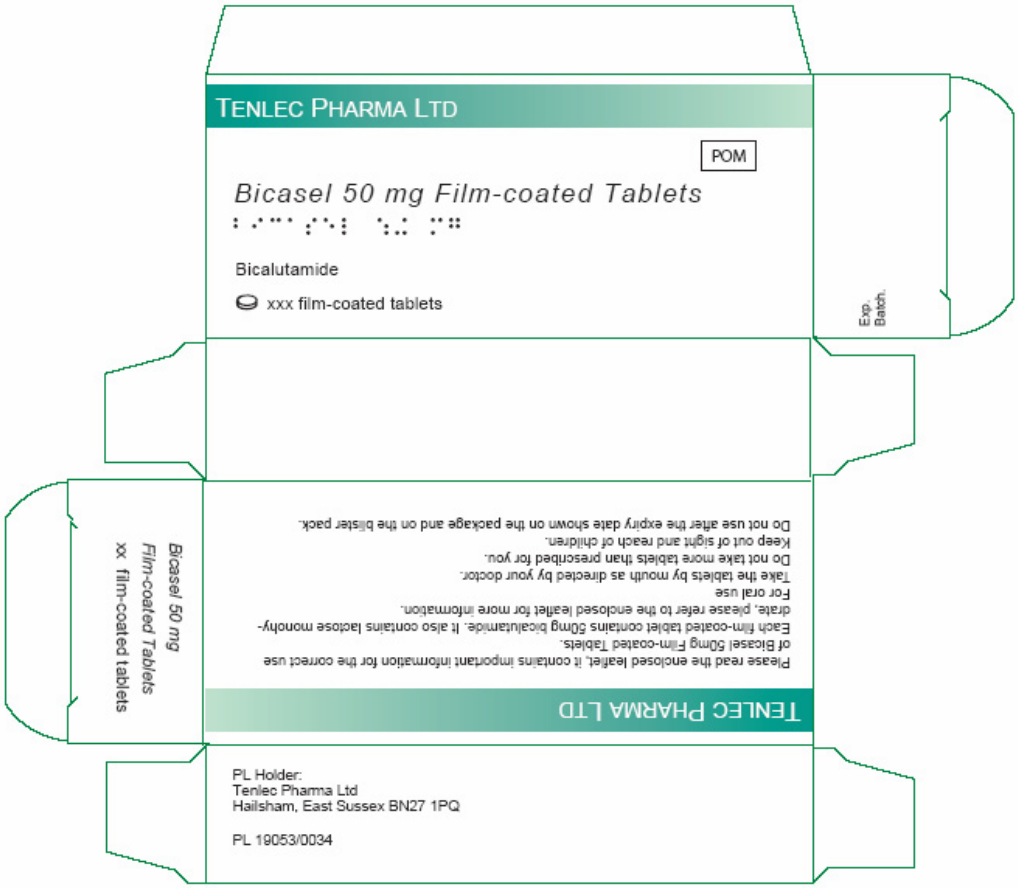

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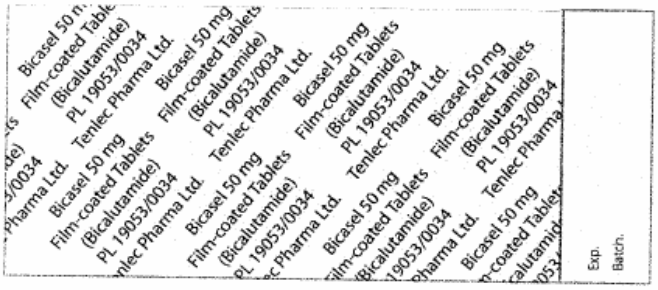

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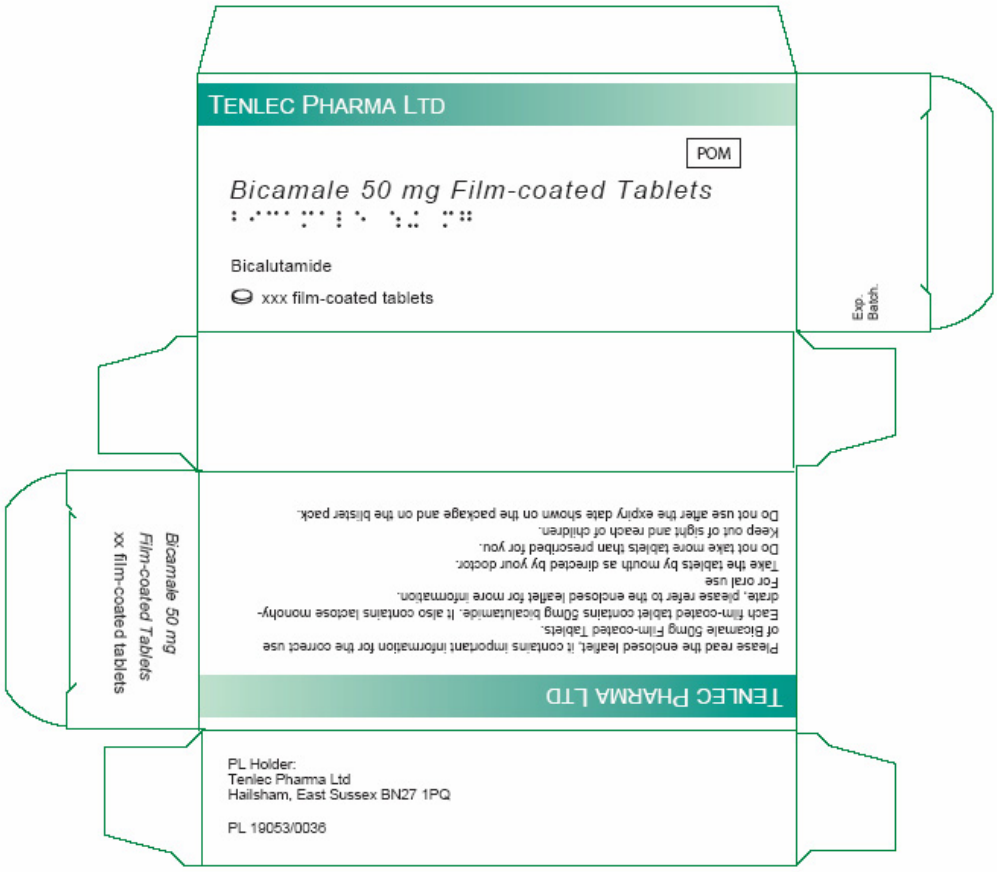

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