SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Casomide 50 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains 50 mg bicalutamide.
Excipient: 1 tablet contains 60 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Advanced prostate cancer
Treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration (daily dose 50 mg bicalutamide).

Locally advanced prostate cancer
Bicalutamide (daily dose 150 mg) is indicated either alone or as adjuvant therapy 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

Posology

Adult males including older people

Advanced prostate cancer
One 50 mg tablet once a day.
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.

Locally advanced prostate cancer
Three 50 mg tablets (150 mg) once a day.
Bicalutamide 150 mg should be taken continuously for at least 2 years or until disease progression.

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

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

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment. Increased accumulation may occur in patients with moderate to severe hepatic impairment (see section 4.4).

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

4.3 Contraindications

- Bicalutamide is contraindicated in females and children (see section 4.6).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Bicalutamide is contraindicated in patients with a history of hepatic toxicity associated with bicalutamide intake.
- Co-administration of terfenadine, astemizole or cisapride with bicalutamide is contraindicated (see section 4.5).

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 suggest that bicalutamide's elimination may be slower in patients with severe hepatic impairment and that this could lead to increased accumulation of bicalutamide. Therefore, bicalutamide should be used with caution in patients with moderate to severe hepatic impairment.

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

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

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes. Consideration should therefore be given to monitoring blood glucose in patients receiving bicalutamide in combination with LHRH agonists.

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).

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.

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating bicalutamide.

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

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence of any pharmacodynamic or pharmacokinetic interactions 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 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 (see section 4.3) and caution should be exercised with the co-administration of bicalutamide with compounds such as ciclosporin and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For ciclosporin, it is recommended that plasma concentrations and clinical condition are closely monitored following initiation or cessation of bicalutamide therapy.

Caution should be exercised when administering bicalutamide to patients taking medicinal products that inhibit the oxidation 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.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of bicalutamide with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

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

4.7 Effects of 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

In this section undesirable effects are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

<u>Blood and lymphatic system disorders</u>
Very common: Anaemia
Very rare: Thrombocytopenia

<u>Immune system disorders</u>
Uncommon: Hypersensitivity reactions, including angioneurotic oedema and urticaria

<u>Metabolism and nutrition disorders</u>
Common: Diabetes mellitus, decreased appetite
Uncommon: Hyperglycaemia, weight loss

<u>Psychiatric disorders</u>
Very common: Decreased libido
Common: Depression

Nervous system disorders
Very common: Dizziness
Common: Somnolence
Uncommon: Insomnia

Cardiac disorders
Common: Myocardial infarction (fatal outcomes have been reported)[6], heart failure[6]
Very rare: Angina, conduction defects including PR and QT interval prolongations, arrhythmias and non-specific ECG changes

Vascular disorders
Very common: Hot flush

Respiratory, thoracic and mediastinal disorders
Uncommon: Interstitial lung disease[4] (fatal outcomes have been reported), dyspnoea

Gastrointestinal disorders
Very common: Abdominal pain, constipation, nausea
Common: Diarrhoea, dyspepsia, flatulence
Uncommon: Dry mouth
Rare: Vomiting

Hepatobiliary disorders
Common: Hepatic changes (elevated levels of transaminases, bilirubinaemia, hepatomegaly, cholestasis and jaundice)[1], hepatotoxicity
Rare: Severe hepatic impairment, hepatic failure[2,5] (fatal outcomes have been reported)

Skin and subcutaneous tissue disorders
Common: Pruritus, dry skin, rash, maculopapular rash, sweating, hirsutism/ hair re-growth, alopecia

Renal and urinary disorders
Very common: Haematuria
Uncommon: Nocturia

Reproductive system and breast disorders
Very common: Erectile dysfunction, impotence, breast tenderness[3], gynaecomastia[3]

General disorders and administration site conditions
Very common: Asthenia, oedema (face, extremities, trunk)
Common: General pain, pelvic pain, chills, chest pain
Uncommon:Headache, pain in the back, neck pain

Investigations
Common: Weight gain
Not known: QT prolongation (see sections 4.4 and 4.5)

[1] Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4).
[2] Hepatic failure has occurred very rarely in patients treated with bicalutamide, but a casual relationship has not been established with certainty. Periodic liver function testing should be considered (see also section 4.4).
[3] May be reduced by concomitant castration.
[4]Listed as an adverse drug reaction following review of post-marketed data. Frequency has been determined from the incidence of reported adverse events of interstitial pneumonia in the randomised treatment period of the 150 mg EPC studies.
[5]Listed as an adverse drug reaction following review of post-marketed data. Frequency has been determined from the incidence of reported adverse events of hepatic failure in patients receiving treatment in the open-label bicalutamide arm of the 150 mg EPC studies.

[6]Observed in a pharmaco-epidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risk appeared to be increased when bicalutamide 50 mg was used in combination with LHRH agonists, but no increase in risk was evident when bicalutamide 150 mg was used as a monotherapy to treat prostate cancer.

In addition, cardiac failure was reported in clinical trials (as a possible adverse drug reaction in the opinion of investigating clinicians, with a frequency of >1%) during treatment with bicalutamide plus an LHRH analogue. There is no evidence of a causal relationship with drug treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is no human experience of overdosage.

Since bicalutamide belongs to the anilide compounds there is a theoretical risk of the development of methaemoglobinaemia. Methaemoglobinaemia has been observed in animals after an overdose. Accordingly, a patient with an acute intoxication can be cyanotic. There is no specific antidote; treatment should be symptomatic.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormone antagonists and related agents, anti-androgens
ATC code: L 02 BB03.

Bicalutamide is a non-steroidal antiandrogen, specific for androgenic receptors, and devoid of all other endocrine activity.
It induces regression of prostate cancer by blocking the activity of androgens at receptor level. Clinically, discontinuation of bicalutamide may result in withdrawal syndrome in certain patients.

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

Bicalutamide 150 mg was studied as a treatment for patients with localised (T1-T2, N0 or NX, M0) or locally advanced (T3-T4, any N, M0; T1-T2, N+, M0) non-metastatic prostate cancer in a combined analysis of 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 to 1.09). 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	Events (%) in bicalutamide patients	Events (%) 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 patient group.

5.2 Pharmacokinetic properties

Bicalutamide is well absorbed following oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.

The (S)-enantiomer is rapidly cleared relative to the (R)-enantiomer, the latter having a plasma elimination half-life of about 1 week.

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

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

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

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

In a clinical study, the mean concentration of the (R)-enantiomer in seminal fluid of men receiving bicalutamide (150 mg/day) was 4.9 µg/mL. The amount of bicalutamide potentially delivered to the

female partner during sexual intercourse is low (approximately 0.3 µg/kg). This is below the threshold which may cause changes in the progeny of laboratory animals.

5.3 Preclinical safety data

Bicalutamide is an androgen receptor antagonist in experimental animals and humans.

The main secondary pharmacological action is induction of CYP450 dependent mixed function oxidases in the liver. Enzyme induction has not been observed in humans. Target organ changes in animals are clearly related to the primary and secondary pharmacological action of bicalutamide. These comprise involution of androgen-dependent tissues; thyroid follicular adenomas, hepatic and Leydig cell hyperplasias and neoplasias or cancer; disturbance of male offspring sexual differentiation; reversible impairment of fertility in males. Genotoxicity studies did not reveal any mutagenic potential of bicalutamide. All adverse effects observed in animal studies are considered to have no relevance to the treatment of patients with advanced prostate cancer.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Sodium starch glycolate (Type A)
Povidone K30
Magnesium stearate

Film-coating:
Titanium dioxide (E171)
Hypromellose
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

7, 10, 14, 15, 28, 30, 50, 56, 60, 84, 90 or 100 tablets in blisters (PVC/aluminium or PVC/PVDC/aluminium)

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

PA0126/174/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th July 2008

10. DATE OF REVISION OF THE TEXT

June 2015