SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME
BICAMIDE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION IN ACTIVE SUBSTANCE
Each film coated tablet contains 50mg of Bicalutamide.

Excipient(s) with known effect:
Each tablet contains 62.7 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablets, white.

4. CLINICAL DATA

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

4.2 Dosage and administration
Route of administration: Oral
Adult males including the elderly: one tablet (50mg) once a day.
Treatment with Bicamide should be started at least 3 days before starting treatment with an LHRH analogue, or at the same time as surgical castration.

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)

Paediatric population: Bicamide is contraindicated for use in children

4.3 Contraindications
Bicamide is contraindicated in females and children.
Bicamide must not be given to any patient who has shown a hypersensitivity reaction to the active substance or any of the excipients listed in section 6.1.
Co-administration of terfenadine, astemizole or cisapride with Bicamide is contra-indicated (see section 4.5)

4.4 Special warnings and special precautions during use
Initiation of treatment should be under the direct supervision of a specialist. Bicamide 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

Bicamide. Therefore, Bicamide 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 Bicamide therapy.

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

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 Bicamide in combination with LHRH agonists.

Bicamide has been shown to inhibit cytochrome P450 (CYP3A4), as such caution should be exercised when co-administered with drugs metabolised predominantly by CYP3A4 (see sections 4.3 and 4.5).

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

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 Bicamide.

4.5 Interactions with other drugs and other forms of interaction
There is no evidence of any pharmacodynamic or pharmacokinetic interactions between Bicamide 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 Bicamide, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of Bicamide 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 Bicamide 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 Bicamide therapy.

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

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

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Bicamide 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).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Pregnasy and lactation
Bicamide 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
Bicamide 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
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).

Table 1 Frequency of Adverse Reactions

System Organ Class	Frequency	Event
Blood and lymphatic system disorders	Very common	Anaemia
Immune system disorders	Uncommon	Hypersensitivity, angioedema and urticaria
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Common	Decreased libido depression
Nervous system disorders	Very common	Dizziness
	Common	Somnolence
Cardiac disorders	Common	Myocardial infarction (fatal outcomes have been reported)[4], Cardiac failure[4]
	Not known	QT prolongation (see sections 4.4 and 4.5).
Vascular disorders	Very common	Hot flush
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung disease[5] (fatal outcomes have been reported).
Gastrointestinal disorders	Very common	Abdominal pain

		constipation nausea
	Common	Dyspepsia flatulence
Hepatobiliary disorders	Common	Hepatotoxicity, jaundice, hypertransaminasaemia[1]
	Rare	Hepatic failure[2] (fatal outcomes have been reported).
Skin and subcutaneous tissue disorders	Common	Alopecia hirsutism/hair re-growth dry skin pruritus rash
	Rare	Photosensitivity reaction
Renal and urinary disorders	Very common	Haematuria
Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness[3]
	Common	Erectile dysfunction
General disorders and administration site conditions	Very common	Asthenia oedema
	Common	Chest pain
Investigations	Common	Weight increased

1. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.

2. 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 Bicamide arm of the 150 mg EPC studies.

3. May be reduced by concomitant castration.

4. 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 Bicamide 50 mg was used in combination with LHRH agonists, but no increase in risk was evident when Bicamide 150 mg was used as a monotherapy to treat prostate cancer.

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 interstitial pneumonia in the randomised treatment period of the 150 mg EPC studies.

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 the Yellow Card Scheme.

4.9 Overdosage

There is no human experience of overdosage. There is no specific antidote; treatment should be symptomatic. Dialysis may not be helpful, since Bicamide 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 Pharmacodynamics

Anti-androgen, ATC code L02 B B03

Bicamide 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 Bicamide can result in antiandrogen withdrawal syndrome in a subset of patients.

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

5.2 Pharmacokinetics

Absorption

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

Distribution

Bicamide 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.

Biotransformation

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 Bicamide, 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 Bicamide. At steady state the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.

Elimination

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

Special Populations

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.

5.3 Preclinical safety data
Bicamide is a potent anti-androgen and a mixed function oxidase enzyme inhibitor 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. PHARMACEUTICS

6.1 Excipients
Lactose monohydrate, Povidone K-25, Sodium starch glycollate, Magnesium stearate, Hypromellose, Titanium dioxide, Propylene glycol.

6.1 Incompatibilities
None known.

6.2 Self life
36 months.

6.4 Special precautions for storage
Store at temperature below 30^0C.

6.5 Nature and contents of container
PVC/ PVDC/Aluminium blisters.

6.6 Instructions for use handling:
There are no specific requirements.

7. MARKETING AUTHORISATION HOLDER
Genepharm S.A.-18th Km Marathonos Avenue-153 51 Pallini Attiki

8. MARKETING AUTHORISATION NUMBER
06077/07220/REN/2020

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