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CALUTIDE Tablets (Bicalutamide)

Composition

Each film-coated tablet contains:
Bicalutamide ..... 50 mg

Dosage Form

Film-coated oral tablet

Pharmacology

Pharmacodynamics

Mechanism of Action
Bicalutamide is a non-steroid anti-androgen; devoid of other endocrine activity. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen.
When bicalutamide is combined with luteinizing hormone-releasing hormone (LHRH) analogue therapy, the suppression of serum testosterone induced by the LHRH analogue is not affected. However, in clinical trials with bicalutamide as a single agent for prostate cancer, rises in serum testosterone and oestradiol have been noted.
In a subset of patients who have been treated with bicalutamide and an LHRH agonist, and who discontinue bicalutamide therapy due to progressive advanced prostate cancer, a reduction in the prostate-specific antigen (PSA) and/or clinical improvement (anti-androgen withdrawal phenomenon) may be observed.

Pharmacokinetics

Absorption
Bicalutamide is well-absorbed following oral administration, although the absolute bioavailability is unknown. Co-administration of bicalutamide with food has no clinically significant effect on the rate or extent of absorption.
Distribution
Bicalutamide is highly protein-bound (96%).
Metabolism/Elimination
Bicalutamide undergoes stereo-specific metabolism. The S (inactive)-isomer is metabolized primarily by glucuronidation. The R (active)-isomer also undergoes glucuronidation but is predominantly oxidized to an inactive metabolite followed by glucuronidation. Both the parent and metabolite glucuronides are eliminated in the urine and faeces. The S-enantiomer is rapidly cleared relative to the R-enantiomer, with the R-enantiomer accounting for about 99% of total steady-state plasma levels.

Pharmacokinetics of the active enantiomer of bicalutamide in normal males and patients with prostate cancer are presented below:

Table 1: Pharmacokinetics of the active enantiomer of bicalutamide

Parameter	**Mean**	**Standard Deviation**
Normal males (n=30)		
Apparent oral clearance (L/hr)	0.320	0.103
Single dose peak concentration (µg/mL)	0.768	0.178
Single-dose time-to-peak concentration (hours)	31.3	14.6
Half-life (days)	5.8	2.29
Patients with prostate cancer (n=40)		
Css* (µg/mL)	8.939	3.504

*Steady-state Concentration

Indication

CALUTIDE tablets are indicated in the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

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.

Bicalutamide 150 mg is also indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention is not considered appropriate or acceptable.

Dosage And Administration

The recommended dose for **CALUTIDE** tablets in combination with an LHRH analogue is one 50 mg tablet once daily (morning or evening), with or without food. It is recommended that **CALUTIDE** tablets be taken at the same time each day.

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

Treatment with **CALUTIDE** should be started at the same time as treatment with an LHRH analog.

Special Populations

Renal impairment

No dose adjustment is necessary for patients with renal impairment.

Hepatic impairment

No dose adjustment is necessary for patients with mild to moderate hepatic impairment. In patients with severe liver impairment (n=4), although there was a 76% increase in the half-life (5.9 and 10.4 days for normal and impaired patients, respectively) of the active enantiomer of bicalutamide no dosage adjustment is necessary.

Contraindications

Hypersensitivity

CALUTIDE tablets are contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the tablet's components. Hypersensitivity reactions including angioneurotic edema and urticaria have been reported

Women

CALUTIDE tablets has no indication for women, and should not be used in this population.

Pregnancy

CALUTIDE Tablets may cause fetal harm when administered to a pregnant woman. **CALUTIDE** is contraindicated in women, including those who are or may become pregnant. There are no studies in pregnant women using **CALUTIDE**. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the fetus.

Warnings And Precautions

Drug Interactions

Clinical studies have not shown any drug interactions between bicalutamide and LHRH analogs (goserelin or leuprolide). 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 cytochrome (CYP) 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity. Clinical studies have shown that with co-administration of bicalutamide, mean midazolam (a CYP 3A4 substrate) levels may be increased 1.5 fold (for C_{max}) and 1.9 fold (for AUC). Hence, caution should be exercised when co-administered with drugs metabolized predominantly by CYP 3A4.
In vitro protein-binding studies have shown that bicalutamide can displace coumarin anticoagulants from binding sites. Prothrombin times should be closely monitored in patients already receiving coumarin anticoagulants who are started on bicalumtamide and adjustment of the anticoagulant dose may be necessary

Renal Impairment

Renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of total bicalutamide or the active R-enantiomer.

Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment. The pharmacokinetics of the (R)-enantiomer are unaffected by mild-to-moderate hepatic impairment. However, bicalutamide is extensively metabolized in the liver. Data suggest 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.
CALUTIDE should be used with caution in patients with moderate-to-severe hepatic impairment. **CALUTIDE** is extensively metabolized by the liver. Limited data in subjects with severe hepatic impairment suggest that excretion of bicalutamide may be delayed and could lead to further accumulation. Periodic liver function tests should be considered for hepatic-impaired patients on long-term therapy.
No clinically significant difference in the pharmacokinetics of either enantiomer of bicalutamide was noted in

patients with mild-to-moderate hepatic disease as compared to healthy controls. However, the half-life of the R-enantiomer was increased approximately 76% (5.9 and 10.4 days for normal and impaired patients, respectively) in patients with severe liver disease (n=4).

Hepatitis

Rare cases of death or hospitalization due to severe liver injury have been reported post-marketing in association with the use of bicalutamide. Hepatotoxicity in these reports generally occurred within the first three to four months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in approximately 1% of bicalutamide patients in controlled clinical trials.
Serum transaminase levels should be measured prior to starting treatment with bicalutamide, at regular intervals for the first four months of treatment, and periodically thereafter. If clinical symptoms or signs suggestive of liver dysfunction occur (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, “flu-like” symptoms, dark urine, jaundice, or right upper quadrant tenderness), the serum transaminases, in particular the serum ALT, should be measured immediately. If at any time a patient has jaundice, or their ALT rises above two times the upper limit of normal, **CALUTIDE** should be immediately discontinued with close follow-up of liver function.

Pregnancy

Pregnancy Category X
Based on its mechanism of action, bicalutamide may cause fetal harm when administered to a pregnant woman. Bicalutamide is contraindicated in women, including those who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
While there are no human data on the use of bicalutamide in pregnancy and bicalutamide is not for use in women, it is important to know that maternal use of an androgen receptor inhibitor could affect development of the fetus.
In animal reproduction studies, male offspring of rats receiving doses of 10 mg/kg/day (approximately 2/3 of clinical exposure at the recommended dose) and above, were observed to have reduced anogenital distance and hypospadias. These pharmacological effects have been observed with other antiandrogens. No other teratogenic effects were observed in rabbits receiving doses up to 200 mg/kg/day (approximately 1/3 of clinical exposure at the recommended dose) or rats receiving doses up to 250 mg/kg/day (approximately 2 times the clinical exposure at the recommended dose).

Lactation

Bicalutamide is not indicated for use in women.

Pediatric use

The safety and effectiveness of bicalutamide in pediatric patients have not been established.
Bicalutamide orodispersible tablet was studied in combination with anastrozole orodispersible tablet in an open-label, non-comparative, multi-center study that assessed the efficacy and safety of this combination regimen over 12 months in the treatment of gonadotropin-independent precocious puberty in boys with familial male-limited precocious puberty, also known as testotoxicosis. Patients were enrolled in the study if they had a baseline age ≥ 2 years and a diagnosis of testotoxicosis based on clinical features of progressive precocious puberty, symmetrical testicular enlargement, advanced bone age, pubertal levels of serum testosterone, prepubertal pattern of gonadotropin secretion following a GnRH stimulation test, and absence of other clinical and biochemical causes of testosterone excess. Thirteen out of the 14 patients enrolled

completed 12 months of combination treatment (one patient was lost to follow-up). If central precocious puberty (CPP) developed an LHRH analog was to be added. Four patients were diagnosed with CPP during the 12-month study and received LHRH analog treatment and 2 additional patients were diagnosed at the end of the 12 months and received treatment subsequently. Mean ± SD characteristics at baseline were as follows: chronological age: 3.9±1.9 years; bone age 8.8±2.5; bone age/chronological age ratio: 2.06 ± 0.51; growth rate (cm/yr): 10.81 ± 4.22; growth rate standard deviation score (SDS): 0.41 ± 1.36.

The starting dose of bicalutamide was 12.5 mg. Bicalutamide was titrated in each patient until steady-state R-bicalutamide (the active isomer of bicalutamide) trough plasma concentration reached 5-15 mcg/mL, which is the range of therapeutic concentrations achieved in adults with prostate cancer following the administration of the currently approved bicalutamide dose of 50 mg. The starting daily dose of anastrozole was 0.5 mg. Anastrozole was independently titrated in each patient until it reached at steady-state a serum estradiol concentration of <10 pmol/L (2.7 pg/mL). The following ascending doses were used for bicalutamide: 12.5 mg, 25 mg, 50 mg, and 100 mg. For anastrozole there were two ascending doses: 0.5 mg and 1 mg. At the end of the titration phase 1 patient was on 12.5 mg bicalutamide, 8 patients were on 50 mg bicalutamide, and 4 patients were on 100 mg bicalutamide; 10 patients were on 1 mg anastrozole. In the majority of patients, steady-state trough concentrations of R-bicalutamide appeared to be attained by Day 21 with once daily dosing. Steady-state trough plasma anastrozole concentrations appeared to be attained by Day 8.

The primary efficacy analysis of the study was to assess the change in growth rate after 12 months of treatment, relative to the growth rate during the ≥6 months prior to entering the study. Pre-study growth rates were obtained retrospectively. There was no statistical evidence that the growth rate was reduced during treatment. During bicalutamide/anastrozole treatment the mean growth rate (cm/yr) decreased by 1.6 cm/year, 95% CI (-4.7 to 1.5) p=0.28; the mean growth rate SDS decreased by 0.1 SD, 95% CI (–1.2 to 1.0) p=0.88. Table 2 shows descriptive data for growth rates for the overall population and for subgroups defined by history of previous treatment for testotoxicosis with ketoconazole, spironolactone, anastrozole or other aromatase inhibitors.

Table 2: Growth rates

Endpoint	Analysis population	Pre-study Mean	Change from pre-study to12 months			% patients with growth reduction [1]
			Mean	Median	(Min, Max)	
Growth rate (cm/yr)	All Treated (n=13)	10.8	-1.6	-2.8	(-7.4, 8.4)	9/13 (69%)
	PT [2] (n=6)	10.3	-0.2	-2.6 [4]	(-7.2, 8.4)	4/6 (67%)
	NPT[3] (n=7)	11.2	-2.8	-2.8	(-7.4, 1.1)	5/7 (71%)
Growth rate (SD units)	All treated (n=13)	0.4	-0.1	-0.4	(-2.7, 3.5)	9/13 (69%)
	PT [2] (n=6)	-0.1	+0.7	-0.2 [4]	(-1.6, 3.5)	4/6 (67%)
	NPT [3](n=7)	0.8	-0.7	-0.4	(-2.7, 0.5)	5/7 (71%)

[1] Change compared to pre-study growth rate
[2] PT = Previous treatment for testotoxicosis with ketoconazole, spironolactone, anastrazole or other aromatase inhibitors
[3] NPT = no previous treatment for testotoxicosis with ketoconazole, spironolactone, anastrozole or other aromatase inhibitors
[4]Median calculated as midpoint of 3rd and 4th ranked observations
Total testosterone concentrations increased by a mean of 5 mmol/L over the 12 months of treatment from a baseline mean of 10 mmol/L. Estradiol concentrations were at or below the level of quantification (9.81 pmol/L) for 11 of 12 patients after 12 months of treatment. Six of the 12 patients started treatment at an estradiol concentration below the level of quantification.
There were no deaths, serious adverse events, or discontinuations due to adverse events during the study. Of the 14 patients exposed to study treatment, 13 (92.9%) experienced at least one adverse event. The most frequently reported (>3 patients) adverse events were gynecomastia (7/14, 50%), central precocious puberty (6/14, 43%), vomiting (5/14, 36%), headache (3/14, 21%), pyrexia (3/14, 21%) and upper respiratory tract infection (3/14, 21%). Adverse reactions considered possibly related to bicalutamide by investigators included gynecomastia (6/14, 43%), central precocious puberty (2/14, 14%), breast tenderness (2/14, 14%), breast pain (1/14, 7%), asthenia (1/14, 7%), increased alanine aminotransferase (1/14, 7%), increased aspartate aminotransferase (1/14, 7%), and musculoskeletal chest pain (1/14, 7%). Headache was the only adverse reaction considered possibly related to anastrazole by investigators. For the patient who developed elevated ALT and AST, the elevation was <3X ULN, and returned to normal without stopping treatment; there was no concomitant elevation in total bilirubin.

Geriatric Use

In two studies in patients given 50 or 150 mg daily, no significant relationship between age and steady-state levels of total bicalutamide or the active R-enantiomer has been shown.

Gynaecomastia and Breast Pain

In clinical trials with bicalutamide 150 mg as a single agent for prostate cancer, gynaecomastia and breast pain have been reported in up to 38% and 39% of patients, respectively.

Glucose Tolerance

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.

Laboratory Tests

Regular assessments of serum PSA may be helpful in monitoring the patient’s response. If the PSA levels rise during bicalutamide therapy, the patient should be evaluated for clinical progression. For patients who have objective progression of disease together with an elevated PSA, a treatment-free period of anti-androgen, while continuing the LHRH analogue, may be considered.

Effects on the Ability to Drive and Use Machines

Bicalutamide 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.

Women

Bicalutamide has not been studied in women.

Undesirable Effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience

In patients with advanced prostate cancer treated with bicalutamide in combination with an LHRH analog, the most frequent adverse reaction was hot flashes (53%).

In the multicenter, double-blind, controlled clinical trial comparing bicalutamide 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analog, the following adverse reactions with an incidence of 5% or greater, regardless of causality, have been reported.

Table 2: Incidence of Adverse Reactions (≥ 5% in Either Treatment Group) Regardless of Causality

Body System Adverse Reaction	**Treatment Group Patients (%) Bicalutamide Plus LHRH Analog (n=401)**	**Number of Flutamide Plus LHRH Analog (n=407)**
Body as a Whole		
Pain (General)	142 (35)	127 (31)
Back Pain	102 (25)	105 (26)
Asthenia	89 (22)	87 (21)
Pelvic Pain	85 (21)	70 (17)
Infection	71(18)	57 (14)
Abdominal Pain	46 (11)	46 (11)
Chest Pain	34 (8)	34(8)
Headache	29 (7)	27(7)
Flu Syndrome	28 (7)	30 (7)
Cardiovascular		
Hot Flashes	211 (53)	217 (53)
Hypertension	34(8)	29(7)
Digestive		
Constipation	87(22)	69(17)
Nausea	62(15)	58(14)
Diarrhea	49(12)	107 (26)
Increased Liver Enzyme Test	30(7)	46(11)

Dyspepsia	30(7)	23 (6)
Flatulence	26(6)	22 (5)
Anorexia	25(6)	29(7)
Vomiting	24(6)	32(8)
Hemic and Lymphatic		
Anemia	45(11)	53(13)
Metabolic and Nutritional		
Peripheral Edema	53(13)	42 (10)
Weight Loss	30 (7)	39(10)
Hyperglycemia	26 (6)	27 (7)
Alkaline Phosphatase Increased	22(5)	24(6)
Weight Gain	22(5)	18(4)
Muscoloskeletal		
Bone Pain	37(9)	43(11)
Myasthenia	27(7)	19(5)
Arthritis	21 (5)	29 (7)
Pathological Fracture	17 (4)	32 (8)
Nervous System		
Dizziness	41 (10)	35 (9)
Paresthesia	31 (8)	40 (10)
Insomnia	27 (7)	39(10)
Anxiety	20(5)	9 (2)
Depression	16(4)	33(8)
Respiratory System		
Dyspnea	51 (13)	32 (8)
Cough Increased	33 (8)	24 (6)
Pharyngitis	32 (8)	23 (6)
Bronchitis	24 (6)	22 (3)
Pneumonia	18 (4)	19 (5)

Rhinitis	15 (4)	22 (5)
Skin and appendages		
Rash	35 (9)	30 (7)
Sweating	25 (6)	20 (5)
Urogenital		
Nocturia	49 (12)	55 (14)
Hematuria	48 (12)	26 (6)
Urinary Tract Infection	35 (9)	36 (9)
Gynecomastia	36 (9)	30 (7)
Impotence	27 (7)	35 (9)
Breast Pain	23(6)	15(4)
Urinary Frequency	23 (6)	29 (7)
Urinary Retention	20 (5)	14 (3)
Urinary Impaired	19 (5)	15 (4)
Urinary Incontinence	15 (4)	32 (8)

Other adverse reactions (greater than or equal to 2%, but less than 5%) reported in the bicalutamide-LHRH analog treatment group are listed below by body system and are in order of decreasing frequency within each body system regardless of causality.

Body as a Whole: Neoplasm; Neck Pain; Fever; Chills; Sepsis; Hernia; Cyst

Cardiovascular: Angina Pectoris; Congestive Heart Failure; Myocardial Infarct; Heart Arrest; Coronary Artery Disorder; Syncope

Digestive: Melena; Rectal Hemorrhage; Dry Mouth; Dysphagia; Gastrointestinal Disorder; Periodontal Abscess; Gastrointestinal Carcinoma

Metabolic and Nutritional: Edema; BUN Increased; Creatinine Increased; Dehydration; Gout; Hypercholesteremia

Musculoskeletal: Myalgia; Leg Cramps

Nervous: Hypertonia; Confusion; Somnolence; Libido Decreased; Neuropathy; Nervousness

Respiratory: Lung Disorder; Asthma; Epistaxis; Sinusitis

Skin and Appendages: Dry Skin; Alopecia; Pruritus; Herpes Zoster; Skin Carcinoma; Skin Disorder

Special Senses: Cataract specified

Urogenital: Dysuria; Urinary Urgency; Hydronephrosis; Urinary Tract Disorder

Abnormal Laboratory Test Values: Laboratory abnormalities including elevated AST, ALT, bilirubin, BUN, and creatinine and decreased hemoglobin and white cell count have been reported in both bicalutamide-LHRH analog treated and flutamide-LHRH analog treated patients.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of bicalutamide. Because

these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Uncommon cases of hypersensitivity reactions, including angioneurotic oedema and urticaria, and uncommon cases of interstitial lung disease, including interstitial pneumonitis and pulmonary fibrosis, have been reported with bicalutamide
Reduction in glucose tolerance, manifesting as diabetes or a loss of glycaemic control in those with pre-existing diabetes, has been reported during treatment with LHRH agonists.
If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.
By reporting side effects you can help provide more information on the safety of this product.

Overdosage

Long-term clinical trials have been conducted with dosages up to 200 mg of bicalutamide daily and these dosages have been well tolerated. A single dose of bicalutamide that results in symptoms of an overdose considered to be life threatening has not been established.
Since bicalutamide belongs to the anilide compounds there is theoretical risk of the development of methemoglobinemia. Methemoglobinemia 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
In the management of an overdose with bicalutamide, vomiting may be induced if the patient is alert. It should be remembered that, in this patient population, multiple drugs may have been taken. Dialysis is not likely to be helpful since bicalutamide is highly protein bound and is extensively metabolized. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

Storage And Handling Instructions

Store below 25^{0}C. Keep **CALUTIDE** and all medicines out of the reach of children.

Packaging Information

CALUTIDE: Pack of 10 tablets
Last updated: *December 2018*
Last reviewed: *December 2018*

CALUTIDE Tablets
