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# CASSOTIDE Tablets (Bicalutamide)

## Composition

**CASSOTIDE Tablets**
Each film-coated tablet contains:
Bicalutamide ..... 50 mg

## Dosage Form

Film-coated oral tablet

## Pharmacology

### ▶ Pharmacodynamics

Bicalutamide is a non-steroid anti-androgen; it has no additional endocrine activity. It is bound to androgen receptors without activating gene expression and thereby inhibits androgen stimulation. The result of this inhibition is the regression of prostate tumours.
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.
Bicalutamide is a racemate, with its anti-androgenic activity being almost exclusively in the (R)-enantiomer.

### ▶ 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 |
| Singledose 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) | | |
| $C_{ss}$(mcg/mL) | 8.939 | 3.504 |

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.

## Indications

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

## Dosage And Administration

The recommended dose for **CASSOTIDE** tablets therapy in combination with an LHRH analogue is one 50 mg tablet once daily (morning or evening), with or without food. It is recommended that **CASSOTIDE tablets** be taken at the same time each day. It is recommended that treatment with **CASSOTIDE** tablets should be started at least 3 days before commencing treatment with an LHRH analogue or at the same time as surgical castration. If a dose of **CASSOTIDE** tablets is missed, take the next dose at the scheduled time. Do not take the missed dose and do not double the next dose.

▶ Special Populations

**Children and adolescents**

Bicalutamide is not indicated in children and adolescents.

**Renal Impairment**

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

**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.

## Contraindications

**CASSOTIDE** tablets are contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the tablet's components.

**CASSOTIDE** tablets are contraindicated in females and children.

Co-administration of terfenadine, astemizole or cisapride with **CASSOTIDE** tablets is contraindicated.

## Warnings And Precautions

▶ General

Initiation of treatment should be under the direct supervision of a specialist.

Periodic liver function testing should be considered due to the possibility of hepatic changes. The majority of changes are expected to occur within the first 6 months of bicalutamide therapy.

Severe hepatic changes and hepatic failure have been observed rarely with bicalutamide. Bicalutamide therapy should be discontinued if changes are severe.

Bicalutamide has been shown to inhibit CYP450 3A4; as such, caution should be exercised when co-administered with drugs metabolized predominantly by CYP 3A4.

▶ Drug Interactions

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.

Although clinical studies using antipyrine as a marker of CYP450 activity showed no evidence of a drug interaction potential with bicalutamide, the 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 bicalutamide with compounds such as ciclosporine and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For ciclosporine, it is recommended that plasma concentrations and clinical condition are closely monitored following initiation or cessation of bicalutamide therapy.

Caution should be exercised when prescribing bicalutamide 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 site. It is, therefore, recommended that if bicalutamide is started in patients who are already receiving coumarin anticoagulants, the prothrombin time should be closely monitored.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of **CASSOTIDE** tablets 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.

▶ Androgen Deprivation Therapy

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 physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Cassotide.

▶ Renal Impairment

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

▶ Hepatic Impairment

No 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.

▶ Pregnancy

**Pregnancy Category X**

Bicalutamide is contraindicated in females and should not be given to pregnant women. Bicalutamide tablets may cause foetal harm when administered to a pregnant woman. Bicalutamide tablets are contraindicated in women, including those who are or may become pregnant. There are no studies in pregnant women using bicalutamide tablets. 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 foetus.

▶ Lactation

Bicalutamide is not indicated for use in women and should not be given to nursing mothers.

▶ Paediatric Use

Bicalutamide is contraindicated for use in children.

▶ Geriatric Use

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

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

▶ 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

No studies on the effect on the ability to drive and use machines have been performed. However, it should be noted that, occasionally, somnolence may occur. Any affected patients should exercise caution.

## Undesirable Effects

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); and very rare (<1/10,000), not known (cannot be estimated from the available data).

**Table 2: Frequency of adverse reactions**

| **System Organ Class** | **Frequency** | Event |
|---|---|---|
| ***Blood and lymphatic system disorders*** | Very common | Anaemia |
| ***Immune system disorders*** | Uncommon | Hypersensitivity reactions (including angioneurotic oedema and urticaria) |
| ***Metabolism and nutrition disorders*** | Common | Decreased appetite, Anorexia |
| ***Psychiatric disorders*** | Common | Decreased libido;depression |
| ***Nervous system disorders*** | Very common | Dizziness, paresthesia, insomnia, anxiety, depression |
| | Common | Somnolence |
| ***Cardiac disorders*** | Common | Myocardial infarction (fatal outcomes have been reported)[4], Cardiac failure[4] |
| | Not known | QT prolongation |
| ***Vascular disorders*** | Very common | Hot flush, hypertension |
| ***Respiratory, thoracic and mediastinal disorders*** | Uncommon | Interstitial lung disease[1] (fatal outcomes have been reported), dysponea, cough increased, pharyngitis, bronchitis, pneumonia, rhinitis |
| ***Gastrointestinal disorders*** | Very common | Abdominal pain, constipation, nausea, diarrhoea, |
| | Common | Dyspepsia, flatulence, vomiting |
| ***Hepatobiliary disorders*** | Common | Hepatotoxicity, jaundice, hypertransaminasaemia[1] |
| | Rare | Hepatic failure[2] (fatal outcomes have been reported) |

| | | |
|---|---|---|
| ***Skin and subcutaneous tissue disorders*** | Common | Alopecia, hirsuitism/hair re-growth, dry skin, pruritus, rash, sweating |
| | Rare | Photosensitivity reaction |
| ***Renal and urinary disorders*** | Very common | Haematuria, nocturia, urinary tract infection, urinary frequency, urinary retention, urinary impaired, urinary continence |
| ***Reproductive system and breast disorders*** | Very common | Gynaecomastia and breast tenderness[3] |
| | Common | Impotence, Erectile dysfunction |
| ***General disorders and administration site conditions*** | Very common | Asthenia, oedema, pain (general), back pain, pelvic pain, infection, headache, flu syndrome |
| | Common | Chest pain |
| ***Investigations*** | Common | Weight gain, weight loss, hyperglycemia, alkaline phosphatase 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 bicalutamide 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 appears to be increased when bicalutamide was used in combination with LHRH agonists but no increase in risk was evident when bicalutamide 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

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, have been seen. Cases of interstitial lung disease (some fatal), including interstitial pneumonitis and pulmonary fibrosis, have been reported with bicalutamide. Interstitial lung disease has been reported most often at doses greater than 50 mg. A few cases of fatal hepatic failure have been reported.
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.

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

## Shelf-Life

2 years

## Storage And Handling Instructions

Store below 25°C. Keep container tightly closed.

## Packaging Information

**CASSOTIDE 50**.....Container pack of 10 tablets
*Last Updated: Jul 2015*
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