

**BICATERO 50 (Bicalutamide Tablets 50mg)**



**Module 1**

BICATERO 50 (Bicalutamide Tablets 50mg)

MODULE 1:

ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION

**1.3 Summary of product characteristics (SmPC)**

1.3.1 Summary of product characteristics (SmPC)



**1.3 Product information:**

**1.3.1 Summary of product characteristics (SmPC)**

The summary of product characteristics of BICATERO 50 (Bicalutamide Tablets 50mg) is given in the following.

**BICATERO 50 (Bicalutamide Tablets 50mg)**



**Module 1**

**SUMMARY OF PRODUCT CHARACTERISTICS**



## **1.5 Product Information**

### **1.5.1 Prescribing Information**

#### **Summary of Product Characteristics**

#### **1. NAME OF THE MEDICINAL PRODUCT**

BICATERO 50 (BICALUTAMIDE TABLETS 50 mg)

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

White colored, round shaped, biconvex film coated tablets, debossed with **2** on one side and **H** on the other side.

#### **3. PHARMACEUTICAL FORM**

Film-coated tablet

#### **4. CLINICAL PARTICULARS**

##### **4.1 Therapeutic indications**

Treatment of advanced prostate cancer in combination with Luteinising Hormone-Releasing Hormone (LHRH) analogue therapy or surgical castration.

##### **4.2 Posology and method of administration**

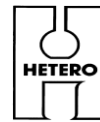
Adult males including the elderly : one tablet (50 mg) once a day.

Treatment with BICATERO should be started at least 3 days before commencing 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

BICATERO is contraindicated for use in children (see section 4.6).

### **4.3 Contraindications**

- BICATERO is contraindicated in women and children (see section 4.6).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Co-administration of terfenadine, astemizole or cisapride with BICATERO is contra-indicated (see section 4.5).

### **4.4 Special warnings and precautions for use**

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

BICATERO 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 BICATERO. Therefore, BICATERO should be used with caution in patients with moderate to severe hepatic impairment.

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

Severe hepatic changes and hepatic failure have been observed rarely with BICATERO, and fatal outcomes have been reported (see section 4.8). BICATERO 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 BICATERO in combination with LHRH agonists.



BICATERO 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).

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 BICATERO.

Antiandrogen therapy may cause morphological changes in spermatozoa. Although the effect of BICATERO on sperm morphology has not been evaluated and no such changes have been reported for patients who received BICATERO, patients and/or their partners should follow adequate contraception during and for 130 days after BICATERO therapy.

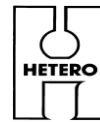
Potential of coumarin anticoagulant effects have been reported in patients receiving concomitant BICATERO therapy, which may result in increased Prothrombin Time (PT) and International Normalised Ratio (INR). Some cases have been associated with risk of bleeding. Close monitoring of PT/INR is advised and anticoagulant dose adjustment should be considered (see sections 4.5 and 4.8).

#### **4.5 Interaction with other medicinal products and other forms of interaction**

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

*In vitro* studies have shown that the (R)-enantiomer of BICATERO 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 BICATERO, mean midazolam exposure (AUC)



was increased by up to 80 %, after co-administration of BICATERO 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 contra-indicated and caution should be exercised with the co-administration of BICATERO 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 BICATERO therapy.

Caution should be exercised when administering BICATERO 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 BICATERO which theoretically could lead to an increase in side effects.

*In vitro* studies have shown that BICATERO can displace the coumarin anticoagulant, warfarin, from its protein binding sites. There have been reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with BICATERO. It is therefore recommended that if BICATERO is administered in patients who are concomitantly receiving coumarin anticoagulants, PT/INR should be closely monitored and adjustments of anticoagulant dose considered (see sections 4.4 and 4.8).

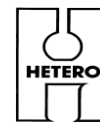
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of BICATERO with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, 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 Fertility, pregnancy and lactation**

##### Pregnancy



BICATERO is contraindicated in females and must not be given to pregnant women.

#### Breast-feeding

BICATERO is contraindicated during breast-feeding.

#### Fertility

Reversible impairment of male fertility has been observed in animal studies (see section 5.3). A period of subfertility or infertility should be assumed in man.

#### **4.7 Effects on ability to drive and use machines**

BICATERO is unlikely to impair the ability of patients to drive or operate machinery. However, it should be noted that occasionally dizziness or somnolence may occur (see section 4.8). Any affected patients should exercise caution.

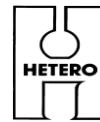
#### **4.8 Undesirable effects**

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

| <b>System Organ Class</b>                | <b>Frequency</b> | <b>Undesirable effect</b>                   |
|--|------------------|---|
| Blood and the lymphatic system disorders | Very Common      | Anaemia                                     |
| Immune system disorders                  | Uncommon         | Hypersensitivity<br>Angioedema<br>Urticaria |
| Metabolism and nutrition disorders       | Common           | Decreased appetite                          |

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|   |             |  |
|---|-------------|--|
| Psychiatric disorders                           | Common      | Decreased libido<br>Depression   |
| Nervous system disorders                        | Common      | Dizziness<br>Somnolence  |
| Cardiac disorders                               | Common      | Myocardial infarction (fatal outcomes                                      |
|   | Not known   | have been reported), cardiac failure                                       |
| Vascular disorders                              | Very Common | Hot flush  |
| Respiratory, thoracic and mediastinal disorders | Uncommon    | Interstitial lung disease <sup>1</sup> (fatal outcomes have been reported) |
| Gastrointestinal disorders                      | Very Common | Abdominal pain<br>Constipation<br>Nausea                                   |
|   | Common      | Dyspepsia<br>Flatulence  |
| Hepato-biliary disorders                        | Common      | Hepatotoxicity<br>Jaundice<br>Hypertransaminasaemia <sup>2</sup>           |
|   | Rare        | Hepatic failure <sup>3</sup> (fatal  |

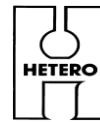


|  |             |   |
|--|-------------|---|
|  |             | outcomes have been reported)  |
| Skin and subcutaneous tissue disorders               | Common      | Rash<br><br>Alopecia<br><br>Hirsutism/hair growth<br><br>Dry skin<br><br>Pruritis |
|  | Rare        | Photosensitivity reaction   |
| Renal and urinary disorders                          | Very Common | Haematuria  |
| Reproductive system and breast disorders             | Very common | Gynaecomastia and breast tenderness <sup>5</sup>                                  |
|  | Common      | Erectile dysfunction  |
| General disorders and administration site conditions | Very common | Asthenia<br><br>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 BICATERO 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 BICATERO 50 mg was used in combination with LHRH agonists, but no increase in risk was evident when BICATERO 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.

Increased PT/INR: Accounts of coumarin anticoagulants interacting with BICATERO have been reported in post marketing surveillance (see sections 4.4. and 4.5).

### **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 Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

### **4.9 Overdose**

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

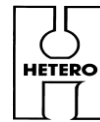
### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Anti-androgen

ATC code: L02BB03

Mechanism of action

BICATERO is a non-steroidal anti-androgen, devoid of other endocrine activity. It binds to the androgen receptors without activating gene expression, and thus inhibits the androgen stimulus.



Regression of prostatic tumours results from this inhibition. Clinically discontinuation of BICATERO can result in the “anti-androgen withdrawal syndrome” in a sub-set of patients.

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

## **5.2 Pharmacokinetic properties**

### Absorption

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

### Distribution

BICATERO 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

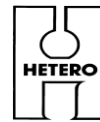
The (S)-enantiomer is rapidly cleared relative to the (R)-enantiomer, the latter having a plasma elimination half-life of about 1 week.

On daily administration of BICATERO, 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 BICATERO. 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-BICATERO in semen of men receiving BICATERO 150 mg was 4.9 microgram/ml. The amount of BICATERO 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

BICATERO 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. Atrophy of seminiferous tubules of the testes is a predicted class effect with antiandrogens and has been observed for all species examined. Reversal of testicular atrophy occurred 4 months after the completion of dosing in a 6-month rat study (at doses of approximately 1.5 times human therapeutic concentrations at the recommended dose of 50 mg). No recovery was observed at 24 weeks after the completion of dosing in a 12-month rat study (at doses of approximately 2 times human concentrations at the recommended human dose of 50 mg). Following 12-months of repeated dosing in dogs (at doses of approximately 7 times human therapeutic concentrations at the recommended human dose of 50 mg), the incidence of testicular atrophy was the same in dosed and control dogs after a 6 month recovery period. In a fertility study (at doses of approximately 1.5 times human therapeutic concentrations at the recommended human dose of 50 mg), male rats had an increased time to successful mating immediately after 11 weeks of dosing; reversal was observed after 7 weeks off-dose.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Lactose monohydrate

Povidone

Crospovidone (type A)

Magnesium stearate

Opadry white-Y-1-7000

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

36 Months (HDPE Container)



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24 Months (Blister Pack)

**6.4 Special precautions for storage**

Store below 30°C and protect from moisture.

**6.5 Nature and contents of container**

30's HDPE Container & 3 x10's Blister pack (Alu-PVC)

**6.6 Special precautions for disposal and other handling**

No special requirements

**7. MARKETING AUTHORISATION HOLDER**

Hetero Labs Limited,

Unit – VI, Sy.No.410 & 411

TSIIC Formulation SEZ

Polepally Village, Jadcherla (Mandal),

Mahaboob Nagar (District), Pin-509301

Telangana, INDIA

Tel No.: +91 08542-238400

**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**