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APPROVED Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

BICALUTAMIDE 50 MG AURO film-coated tablet

BICALUTAMIDE 150 MG AURO film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BICALUTAMIDE 50 MGAURO

Each film coated tablet contains Bicalutamide 50 mg.

Contains sugar: Lactose 61 mg per tablet.

BICALUTAMIDE 150 MG AURO

Each film coated tablet contains Bicalutamide 50 mg.

Contains sugar: Lactose 183 mg per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

BICALUTAMIDE 50 MG AURO Round, white film coated tablets debossed with “B” on one side and “I” on the other side.

BICALUTAMIDE 150 MG AURO White, biconvex, round, film-coated tablet, debossed with 'E150' on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

BICALUTAMIDE 50 MG AURO is indicated for:

• The treatment of advanced prostate cancer in combination with Luteinising Hormone Release Hormone (LHRH) analogue therapy or surgical castration.

BICALUTAMIDE 150 MG AURO is indicated:

In patients with locally advanced prostate cancer (T3-4, any N, M0/T1-2, N+, M0)

• as immediate therapy either alone or as adjuvant to treatment by radical prostatectomy or radiotherapy.

• as monotherapy for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical or medical castration is not appropriate.

4.2 Posology and method of administration

Posology

BICALUTAMIDE 50 MG AURO:

Adult males (including the elderly):

One tablet (50 mg) once daily. Treatment with **BICALUTAMIDE 50 mg AURO** should be started at least three days prior to commencing treatment with a LHRH analogue, or at the same time as surgical castration.

BICALUTAMIDE 150 MG AURO:

Adult males (including the elderly):

One tablet (150 mg) once daily for two years or until progression.

Renal impairment:

No dosage adjustments required.

Hepatic impairment:

No dosage reduction required for patients with mild hepatic impairment. Increased accumulation may occur in patients with moderate to severe impairment.

4.3 Contraindications

BICALUTAMIDE AURO is contraindicated in:

- Patients with a known hypersensitivity towards bicalutamide or any of the excipients of **BICALUTAMIDE AURO**
- Females
- Children
- Pregnant women
- Nursing mothers
- Co-administration of terfenadine, astemizole or cisapride with **BICALUTAMIDE AURO** (see section 4.5)

4.4 Special warnings and precautions for use

Initiation of treatment should be under the direct supervision of an oncologist.

BICALUTAMIDE AURO 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 **BICALUTAMIDE AURO** . Therefore, **BICALUTAMIDE AURO** 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 **BICALUTAMIDE AURO** therapy.

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

Bicalutamide 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).

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 medicines that might prolong the QT interval (see section 4.5) medical practitioners should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating **BICALUTAMIDE AURO**.

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

Potentiation of coumarin anticoagulant effects have been reported in patients receiving concomitant bicalutamide 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).

BICALUTAMIDE AURO contains lactose

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between **BICALUTAMIDE AURO** 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 bicalutamide, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of bicalutamide for 28 days. For medicines 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 AURO** 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 AURO** therapy.

Caution should be exercised when prescribing **BICALUTAMIDE AURO** with other medicines which may inhibit drug oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of **BICALUTAMIDE AURO** 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 sites. There have been reports of increased effect of

warfarin and other coumarin anticoagulants when co-administered with bicalutamide. It is therefore recommended that if **BICALUTAMIDE AURO** 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 **BICALUTAMIDE AURO** with medicines known to prolong the QT interval or medicines able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicines , methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

BICALUTAMIDE AURO is contraindicated in during breastfeeding.

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

BICALUTAMIDE AURO 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

a) Tabulated list of adverse reactions

System Organ Class	Adverse effect	Frequency
Infections and infestations	Frequent	infection, including pulmonary and upper respiratory tract infection
Blood and Lymphatic System Disorders	Frequent	anaemia
	Less frequent	thrombocytopenia, leukopenia, neutropenia
Immune System Disorders	Less frequent	hypersensitivity, angioedema, urticaria
Metabolism and nutrition disorders	Frequent	decrease in or loss of appetite
	Frequency unknown	diabetes mellitus, hyperglycaemia
Psychiatric disorders	Frequent	decreased libido, depression
Gastrointestinal Disorders	Frequent	abdominal pain, nausea, dyspepsia, constipation, diarrhoea, flatulence
	Less frequent	vomiting, gastrointestinal or rectal bleeding, bloated feeling, gas or indigestion
	Frequency unknown	anorexia

Hepatobiliary Disorders	Frequent	hepatotoxicity, jaundice, including cholestatic jaundice, hypertransaminasaemia[1], non-alcoholic fatty liver disease and associated liver disease
	Less frequent	hepatitis, methaemoglobinaemia, hepatic failure* (fatal outcomes have been reported)
Nervous system disorders	Frequent	dizziness, somnolence
	Less frequent	fever, neuromuscular symptoms or neuropathy, confusion, dryness of mouth, nervousness
Cardiac disorders	Frequent	myocardial infarct (fatal outcomes have been reported) [4], cardiac failure4

	Less frequent	hypertension
	Frequency unknown	angina, conduction defects including PR and QT interval prolongation, dysrhythmias and non-specific ECG changes
Vascular disorders	Frequent	hot flushes
Respiratory, thoracic and mediastinal disorders	Less frequent	interstitial lung disease[5] (fatal outcomes have been reported), dyspnoea pulmonary disorder runny nose sore throat tightness in chest
Skin and subcutaneous tissue disorders	Frequent	alopecia, hirsutism/ hair re-growth, dry skin, pruritus, rash
	Less frequent	photosensitivity reaction itching of skin

	Frequency unknown	sweating
Renal and urinary disorders	Frequent	haematuria
	Frequency unknown	nocturia
Reproductive system and breast disorders	Frequent	gynaecomastia, breast tenderness[3], erectile dysfunction
General disorder	Frequent	weakness (asthenia), oedema, chest pain
	Less frequent	chills, drowsiness, flu-like syndrome, headache
Investigations	Frequent	weight increase

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 AURO** 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 **BICALUTAMIDE 50 mg AURO** was used in combination with LHRH agonists, but no increase in risk was evident when **BICALUTAMIDE 150 mg AURO** 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 **BICALUTAMIDE AURO** 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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 **BICALUTAMIDE AURO** 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

A.21.12 Hormone inhibitors.

ATC code: L02BB03

Mechanism of action:

Bicalutamide is a non-steroidal anti-androgen without any other endocrine activity. It binds to androgen receptors without activating gene expression and thus exhibits androgen stimulation. The inhibition of the androgen stimulus results in the regression of prostatic tumours. Bicalutamide is a racemate with the (R)-enantiomer exclusively responsible for the anti-androgen activity.

5.2 Pharmacokinetic properties

Absorption:

Bicalutamide is well absorbed after oral administration and is 96 % bound to plasma protein. Food has not proven to significantly affect the extent of bioavailability of bicalutamide.

Distribution

Bicalutamide 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:

Bicalutamide undergoes extensive metabolism in the liver, the active (R)-enantiomer predominately by oxidation. The half-life of the (R)-enantiomer is about 6-7 days and may be prolonged still further in severe hepatic impairment.

Elimination

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate Ph. Eur

Sodium starch Glycolate (Type A) Ph. Eur. 7

Povidone Ph.Eur

Purified water Ph.Eur

Magnesium stearate Ph.Eur

Opadry@ complete film coating system

02B58900 white IH (HPMC 2910/HYPROMELLOSE, TITANIUM DIOXIDE, MACROGOL/PEG)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister Pack

Clear 250 micron PVC film - aluminium foil blister pack:

Blister pack comprises of Clear 250 micron PVC film as the forming material and 25 micron aluminium foil as the lidding material.

Clear 250 micron PVC/PVDC film - aluminium foil blister pack:

Blister pack comprises of Clear 250 micron PVC film as the forming material and 25 micron aluminium foil as the lidding material.

Package leaflets will be packed into preprinted cartons

Pack size: 10s

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Aurogen South Africa (Pty) Ltd.

Woodhill Office Park, Building 1,

53 Phillip Engelbrecht Avenue,

Meyersdal, Ext. 12,

1448, Johannesburg,

South Africa.

8 REGISTRATION NUMBER(S)

BICALUTAMIDE 50 MG AURO: 59/21.12/0748

BICALUTAMIDE 150 MG AURO: 59/21.12/0749

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

21 JULY 2026

10 DATE OF REVISION OF THE TEXT