BICALUTAMIDA KEMEX®
BICALUTAMIDE 50 mg
Coated Tablets

Made in Argentina **Under prescription only**

1. Name of the medicinal product
Bicalutamida Kemex 50 mg Coated Tablets.

2. Qualitative and quantitative composition
Each coated tablet contains:
Bicalutamide 50 mg; Lactose 61 mg; Sodium starch glycolate 7.5 mg; Povidone K 80 18 mg; Magnesium Stearate 3.6 mg; Methocel 4.3 mg; Titanium dioxide 4.3 mg; Propylene glycol 1.05 mg; Talc 4.3 mg.

3. Pharmaceutical form
Coated tablet.

4. Clinical particulars
4.1 Therapeutic indications
Treatment of advanced prostate cancer in combination with luteinizing-hormone releasing hormone (LHRH) analogue therapy or surgical castration.

4.2 Posology and method of administration
Posology
Adult males including the elderly: one tablet (50 mg) once a day.

Treatment with Bicalutamida Kemex should be started at least 3 days before commencing treatment with an LHRH analogue, or atthe 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: Bicalutamida Kemex is contraindicated for use in children (see section 4.3).

4.3 Contraindications
Bicalutamida Kemex is contraindicated in females 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 Bicalutamida Kemex is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use
Initiation of treatment should be under the direct supervision of a specialist.
Bicalutamida Kemex 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 Bicalutamida Kemex. Therefore, Bicalutamida Kemex 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 Bicalutamida Kemex therapy.
Severe hepatic changes and hepatic failure have been observed rarely with Bicalutamida Kemex, and fatal outcomes have been reported (see section 4.8). Bicalutamida Kemex 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 Bicalutamida Kemex in combination with LHRH agonists.
Bicalutamida Kemex 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 medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potentialfor Torsade de pointes prior to initiating Bicalutamida Kemex.
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 Bicalutamida Kemex, patients and/or their partners should follow adequate contraception during and for 130 days after Bicalutamida Kemex therapy.
Potentiation of coumarin anticoagulant effects have been reported in patients receiving concomitant Bicalutamida Kemex therapy, which may result in increased Prothrombin Time (PT) and International Normalised Ratio (INR). Some cases have beenassociated 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).
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactosemalabsorption 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 medicinal products and other forms of interaction
There is no evidence of any pharmacodynamic or pharmacokinetic interactions between Bicalutamida Kemex 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 Bicalutamida Kemex, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of Bicalutamida Kemex 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 Bicalutamida Kemex 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 Bicalutamida Kemex therapy.
Caution should be exercised when prescribing Bicalutamida Kemex with other drugs which may inhibit drug oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of Bicalutamida Kemex 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 Bicalutamida Kemex. It is therefore recommended that if Bicalutamida Kemex is administered in patients who are concomitantly receiving coumarin anticoagulants, PT/INR should be closely monitored and adjustments of anticoagulant dose considered (seesections 4.4 and 4.8).
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Bicalutamida Kemex 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
Bicalutamide is contraindicated in females and must not be given to pregnant women.
Breast-feeding
Bicalutamide 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
Bicalutamida Kemex 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 theavailable data).

Table 1 Frequency of Adverse Reactions

System Organ Class	Frequency	Event
Blood and lymphatic system disorders	Very common	Anemia
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 Common	Dizziness Somnolence
Cardiac disorders	Common Not know	Myocarial infraction (fatal outcomes have been reported)[4], cardiac failure[4] QT prolongation (see sectione 4.4 and 4.5)
Vascular disorders	Very common	Hot flush
Repiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung desease[5] (fatal outcomes hace been reported).
Gastrointestinal disorders	Very common Common	Abdominal pain, constipation, nausea Dysepsia, flatulence

Hepatobiliary disorders	Common Rare	Hepatotoxicity, jaundice, hypertransaminasaemia[1] Hepatic failure[2] (fatal outcomes have been reported).
Skin and subcutaneous tissue disorders	Common Rare	Alopecia, hirsutism/hair re-growth, dry skin, pruritus, rash Photosensitivity reaction
Renal and urinary disorders	Very common	Haematuria
Reproductive system and breast disorders	Very common Common	Gynaecomastia and breast tenderness[3] Erectile dysfunction
General disorders and administration site conditions	Very common Common	Asthenia, oedema 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 Bicalutamida Kemex 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 Bicalutamida Kemex 50 mg was used in combination with LHRH agonists, but no increase in risk was evident when Bicalutamida Kemex 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 Bicalutamida Kemex 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.

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 Bicalutamida Kemex 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-androgens, ATC code L02BB03

Mechanism of action
Bicalutamida Kemex 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 Bicalutamida Kemex can result in antiandrogen withdrawal syndrome in a subset of patients.
Bicalutamida Kemex is a racemate with its antiandrogenic activity being almost exclusively in the (R)-enantiomer.

5.2 Pharmacokinetic properties
Absorption
Bicalutamida Kemex is well absorbed following oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.
Distribution
Bicalutamida Kemex 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.
Biotranformation
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 Bicalutamida Kemex, 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 Bicalutamida Kemex. At steady state the predominantly active (R)-enantiomer accounts for 99% ofthe total circulating enantiomers.
Elimination
In a clinical study the mean concentration of R-bicalutamide in semen of men receiving Bicalutamida Kemex 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
Bicalutamide 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
Bicalutamida Kemex includes the following excipients:
Lactose
Sodium starch glycolate
Povidone K 80
Magnesium Stearate
Methocel
Titanium dioxide
Propylene glycol
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store at room temperature between 15 and 30 °C

6.5 Nature and contents of container
Available in colorless aluminium-PVC/PVDC blister, containing 14 coated tablets.

6.6 Special precautions for disposal and other handling
No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
Laboratorio Kemex S.A.
Nazarre 3446 (C1417DXH)
Autonomous City of Buenos Aires – Argentina

8. Marketing authorisation number(s)
Certificate No. 48,503

9. Date of first authorisation/renewal of the authorisation
Date of first authorisation: 09 February 2000
Date of last renewal: 09 February 2025

10. Date of revision of the text
October 2017

"THIS MEDICATION MUST BE ADMINISTERED UNDER MEDICAL PRESCRIPTION AND CANNOT BE REPEATED WITHOUT A NEW PRESCRIPTION".
MEDICATION: KEEP AWAY FROM CHILDREN

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