New Zealand Datasheet

1 PRODUCT NAME
Binarex

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Bicalutamide 50 mg film coated tablets

3 PHARMACEUTICAL FORM
Binarex tablets are white to off-white, circular, biconvex, film coated tablets either debossed with "50" on one side and plain on the other side or plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Advanced prostate cancer in combination with GnRH luteinizing-hormone releasing hormone (LHRH) agonist therapy or surgical castration.

Prevention of disease flare associated with the use of LHRH agonists.

4.2 Dose and method of administration
Adult males (including elderly patients) as combination therapy
One 50 mg tablet to be taken once per day.

Therapy with Binarex film coated tablets should be introduced with the initiation of treatment with surgical castration or a GnRH (LHRH) agonist.

Children
Binarex film coated tablets are not recommended for children.

Renal Impairment (in adult males)
No dosage change is advised.

Hepatic Impairment (in adult males)
No dosage change is advised for adult male patients with hepatic impairment that is considered mild. Adult male patients with hepatic impairment that is considered moderate to severe may have increased accumulation (see section 4.4).

4.3 Contraindications
Binarex film coated tablets should not be used in females or children.

Identified hypersensitivity to bicalutamide or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use
Bicalutamide is metabolised in the liver predominantly. For patients who have severe hepatic impairment, observation has suggested that the elimination of bicalutamide may be reduced and this could potentially result in an increase of bicalutamide accumulation. Consequently, Binarex film coated tablets should be administered with care in patients who experience moderate to severe hepatic impairment.

Severe hepatic changes have been rarely detected with bicalutamide treatment, and there have been reports of fatal outcomes (see section 4.8). If hepatic changes are considered severe, Binarex film coated tablet treatment should be discontinued immediately.

In male adults who are taking LHRH agonists, a decrease in glucose tolerance has been reported. This may present as diabetes or for those patients with pre-existing diabetes, a loss of glycaemic control. Therefore, in patients taking Binarex film coated tablets alongside LHRH agonists, care in monitoring blood glucose should be taken.

The QT interval may be extended with androgen deprivation therapy; however, an underlying association has not been recognised with bicalutamide. For patients who have a history of QT prolongation or who have QT prolongation risk factors and in patients taking concomitant medication that may extend the QT interval (see section 4.5), doctors should evaluate the benefit/risk ratio including the possibility of Torsade de Pointes before initiating bicalutamide treatment.

Antiandrogen treatment may result in sperm morphology changes. As the sperm morphology effect from bicalutamide has not been calculated and no changes of this effect have been recorded for patients taking bicalutamide, patients and/or their partners should use contraception methods while taking bicalutamide and for a recommended 130 days following treatment.

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

4.5 Interaction with other medicines and other forms of interaction

No evidence is available between bicalutamide tablets and GnRH analogues for any pharmacodynamic or pharmacokinetic interactions.

It has been suggested that bicalutamide has the potential to inhibit cytochrome 3A4 in studies (*in vitro)*, however, some clinical studies have shown the extent of inhibition is doubtful to be of any clinical importance.

It has been shown in *in vitro* studies, that the coumarin anticoagulant (warfarin) can be displaced by bicalutamide from its protein binding sites.

When bicalutamide is administered together with warfarin and other coumarin anticoagulants, there have been observations of effect increases. Therefore, if bicalutamide is given to patients who are taking coumarin anticoagulants, it is advised that PT/INR should be checked and dosage adjustments of the anticoagulant reviewed (see sections 4.4 and 4.8).

While there is no indication of pharmacodynamic or pharmacokinetic interactions while at steady state between bicalutamide 50 mg and LHRH agonists, bicalutamide 50 mg could possibly avert the damaging clinical outcomes of flare in relation to the initiation of

LHRH agonist treatment.

The use of bicalutamide alongside medication that is recognised to lengthen the QT interval, or medication that is known to induce Torsade de Pointes, must be vigilantly monitored as it is known that androgen deprivation therapy may lengthen the QT interval (see section 4.4).

4.6 Fertility, pregnancy and lactation

Use in pregnancy
Bicalutamide should not be used in pregnancy.

Use in Lactation
Bicalutamide should not be used in mothers who are breastfeeding.

Fertility
In animal studies, reversible male fertility impairment has been reported (see section 5.3). For men, an interval of infertility or subfertility should be expected.

4.7 Effects on ability to drive and use machines

Please note that somnolence has been observed with the usage of bicalutamide and therefore care must be taken when driving or operating machinery if this symptom continues.

4.8 Undesirable effects

The below frequency categories (except if detailed) were determined from the number of adverse effects observed in the pivotal LHRH combination study (bicalutamide 50 mg plus LHRH analogue arm).

Adverse reactions are graded under title of frequency using the following principle: very common ≥ 10%; common ≥ 1% to < 10%; uncommon ≥ 0.1% to < 0.01%; rare ≥ 0.01% to < 0.1% and very rare < 0.01%, including isolated reports.

Frequency	**Description of Adverse Effect**
Blood and Lymphatic Disorders	
Very Common:	Anaemia
Cardiac Disorders	
Common:	Myocardial infarction* where there have been reports of fatal outcomes and cardiac failure
Gastrointestinal Disorders	
Very Common:	Constipation, abdominal pain and nausea
Common:	Flatulence and dyspepsia
General Disorders and Administration Site Conditions	
Very Common:	Asthenia, oedema
Common:	Chest pain

Hepato-biliary Disorders	
Common:	Jaundice, hepatotoxicity and hypertransaminasaemia**
Rare:	Hepatic failure*** where there have been reports of fatal outcomes.
Immune System Disorders	
Uncommon:	Hypersensitivityangiodema and urticaria
Investigations	
Common:	Weight increased
Metabolism and Nutrition Disorders	
Common:	Decreased Appetite
Nervous System Disorders	
Very Common:	Dizziness
Common:	Somnolence
Psychiatric Disorders	
Common:	Depression and decreased libido
Renal and Urinary Disorders	
Very Common:	Haematuria
Reproductive System and Breast Disorders	
Very Common:	Gynaecomastia**** and breast tenderness
Common:	Erectile dysfunction
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon:	Interstitial lung disease***** where there have been reports of fatal outcomes
Skin and Subcutaneous Tissue Disorders	
Common:	Alopecia, rash, hair regrowth/hirsutism, pruritus and dry skin
Vascular Disorders	
Very Common:	Hot flush

* Detected in a pharmaco-epidemiology study in the treatment of prostate cancer (LHRH agonists and anti-androgens). When bicalutamide (50mg) was administered in combination with LHRH agonists, the risk appeared to increase.

** Hepatic changes tended to be often transient and were severe on rare occasions. These changes resolved or improved with continuous treatment or after the end of treatment.

*** Recorded as an adverse effect following the analysis of post-marketed information. The incidence of observed adverse effects has determined the frequency of hepatic failure in people having treatment in the EPC studies (150 mg) open-label bicalutamide arm.

**** May be decreased via concomitant castration.

***** Recorded as an adverse effect following the analysis of post-marketed information. The incidence of observed adverse effects has determined the frequency of interstitial pneumonia in the EPC studies (150 mg) randomised therapy period.

Increased PT/INR: Versions of coumarin anticoagulants working together with bicalutamide have been observed in post marketing analysis (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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose
There are no reports or experience of overdose in humans. There are no specific antidotes to an overdose of bicalutamide and therefore treatment should be symptomatic. As bicalutamide is bound highly to protein and is not found to be unchanged in the urine, dialysis may not be useful. General supportive care, incorporating regular observation of vital signs and close monitoring of the patient is indicated.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anti-androgens, ATC code L02BB03

Bicalutamide is an anti-androgen that is non-steroidal and is lacking of further endocrine activity. Bicalutamide inhibits the androgen stimulus by binding to androgen receptors (without activating gene expression). As a result of this inhibition, deterioration of prostatic tumours occurs. In a number of patients, the withdrawal of bicalutamide treatment can clinically result in antiandrogen withdrawal syndrome.

Bicalutamide is a racemate due to its antiandrogenic action being nearly completely in the (R)-enantiomer.

5.2 Pharmacokinetic properties
Following administration orally, bicalutamide is well absorbed. There is no clinical evidence of food effect on bioavailability.

The (S)-enantiomer is promptly eliminated comparative to the (R)-enantiomer, which has an elimination plasma half-life of approximately one week.

Due to its extended half-life, the (R)-enantiomer of bicalutamide accrues around 10 times in plasma with administration on a daily basis.

Administration daily of bicalutamide (50 mg dosages) results in (R)-enantiomer steady state plasma concentrations of around 9 µg per mL.

While at steady state the (R)-enantiomer pharmacokinetics are unchanged by renal or hepatic (mild to moderate) impairment or age. Please note that for patients with severe hepatic impairment, there is data that shows that the (R)-enantiomer is eliminated more slowly from the plasma.

Bicalutamide metabolites are excreted via the kidneys and bile in mainly equal quantities. Bicalutamide is amply protein bound (racemate 96%, (R)-bicalutamide 99.6%) and also significantly metabolised through oxidation and glucuronidation.

In a clinical study, the semen of male patients showed the (R)-bicalutamide mean concentration receiving bicalutamide 150 mg was 4.9 µg/mL. The quantity of bicalutamide possibly transported during intercourse to a female partner is small (0.3 µg/kg). This level is lower than what is required to cause changes in laboratory animals offspring.

5.3 Preclinical safety data

In animals, bicalutamide is a powerful antiandrogen and a mixed function oxidase enzyme inducer. Organ modifications, involving tumour induction and small clinical pathology changes, are connected to these actions. Enzyme induction and minor cardiac changes observed in dogs have not been reported in humans. For anti-androgens, atrophy of seminiferous tubules of the testes is an expected effect. This has been reported for all species observed.

In a rat study completed over a duration of six months, testicular atrophy reversal followed after four months of discontinuing the dose. Dosages were approximately 1.5 or 0.6 times the therapeutic concentrations recommended for humans at 50 mg or 150 mg, respectively.

In a rat study completed over a duration of twelve months, no recovery was reported after the discontinuation of the dose. Dosages were approximately 2 or 1.9 times the therapeutic concentrations recommended for humans at 50 mg or 150 mg, respectively.

In a dog study completed over a duration of twelve months (with doses being repeated), the testicular atrophy incidence was identical in dogs that were given bicalutamide and the control dogs following a six-month period of recovery. Dosages were approximately 7 or 3 times the therapeutic concentrations recommended for humans at 50 mg or 150 mg, respectively.

In a rat fertility study, male rats took longer to mate successfully immediately after bicalutamide dosing for eleven weeks. Reversal of this effect was reported after seven weeks without bicalutamide. Dosages were approximately 1.5 or 0.6 times human therapeutic concentrations at the recommend human does of 50 mg or 150 mg, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, Crospovidone, Lactose monohydrate, Magnesium stearate, Maize starch, Opadry white Y-1-7000, Povidone, Sodium laurilsulfate.

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf life is 24 months (2 years) from manufacture.

6.4 Special precautions for storage
Store at or below 25°C.

6.5 Nature and contents of container
PVC/Al/VMCH blister packs of 28 tablets or 30 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MEDICINE SCHEDULE
Prescription Medicine.

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9 DATE OF FIRST APPROVAL
22 February 2007

10 DATE OF REVISION OF THE TEXT
1 October 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
3	Additional tablet description
6.5	Addition of 30 tablet pack size.