New Zealand Data Sheet

1. PRODUCT NAME

BICALOX® film-coated tablet, 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BICALOX tablet contains bicalutamide 50 mg.

Excipient(s) with known effect

BICALOX tablets contain lactose. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

BICALOX 50 mg is a white to off-white, round, film coated, biconvex tablets, engraved with 'BC 50' on one face and plain on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of advanced prostate cancer in combination with GnRH (LHRH) agonist therapy or surgical castration.

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

4.2. Dose and method of administration

Dose

As combination therapy in adult males including the elderly

One tablet (50 mg) once a day.

Treatment with BICALOX should be started at the same time as treatment with a GnRH (LHRH) agonist or surgical castration.

Paediatric population

BICALOX is contraindicated in children.

Use in adult males with renal impairment

No dosage adjustment is necessary for patients with renal impairment.

Use in adult males with 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).

4.3. Contraindications

BICALOX is contraindicated in females and children.

BICALOX must not be given to any patient who has shown a hypersensitivity reaction to the active substance or to any of the excipients.

Co-administration of terfenadine, astemizole or cisapride with BICALOX is contraindicated (see section 4.4).

4.4. Special warnings and precautions for use

Bicalutamide is extensively metabolised 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, BICALOX 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 BICALOX therapy.

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

BICALOX has 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, although a causal association has not been established with BICALOX. In patients with a history of or who have risk factors for QT prolongation and in patients receiving concomitant medicinal products that may 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 BICALOX.

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 BICALOX, patients and/or their partners should use adequate contraception methods during and for 130 days after BICALOX therapy.

Potentiation of coumarin anticoagulant effects have been reported in patients receiving concomitant BICALOX 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 medicines and other forms of interaction

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide and GnRH analogues.

In vitro studies have shown that R-bicalutamide is an inhibitor of CYP3A4, 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 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 bicalutamide 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 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 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 is started in patients who are already receiving coumarin anticoagulants, PT/INR should be closely monitored and adjustment of anticoagulant dose considered (see sections 4.4 and 4.8).

Although there is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide and LHRH agonists at steady state, bicalutamide 50 mg may prevent the harmful clinical consequences of flare associated with the start of LHRH agonist therapy.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of BICALOX with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de Pointes should be carefully evaluated (see section 4.4).

4.6. Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

BICALOX is contraindicated in females and must not be given to nursing mothers.

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

During treatment with BICALOX, somnolence has been reported and those patients who experience this symptom should observe caution when driving or using machines.

4.8. Undesirable effects

Unless specified, the following frequency categories were assigned based on the incidence of the adverse event in the 50 mg bicalutamide plus LHRH analogue arm of the pivotal LHRH combination study.

Frequency	System Organ Class	Event
Very common (≥ 10%)	Blood and lymphatic	Anaemia
	Nervous system disorders	Dizziness
	Vascular disorders	Hot flush
	Gastrointestinal disorders	Abdominal pain, constipation, nausea
	Renal and urinary disorders	Haematuria
	Reproductive system and breast disorders	Gynaecomastia and breast tenderness[a]
	General disorders and administration site conditions	Asthenia, oedema

Common (≥ 1% and < 10%)	Metabolism and nutrition disorders	Decreased appetite
	Psychiatric disorders	Decreased libido, depression
	Nervous system disorders	Somnolence
	Cardiac disorders	Myocardial infarction (fatal outcomes have been reported)[e], Cardiac failure[e]
	Gastrointestinal disorders	Dyspepsia, flatulence
	Hepatobiliary disorders	Hepatotoxicity, jaundice, hypertransaminasaemia[b]
	Skin and subcutaneous tissue disorders	Alopecia, hirsutism/ hair regrowth, rash, dry skin, pruritus
	Reproductive system and breast disorders	Erectile dysfunction
	General disorders and administration site conditions	Chest pain
	Investigations	Weight increased
Uncommon (≥ 0.1% and < 1%)	Immune system disorders	Hypersensitivity, angioedema, and urticaria
	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[c]. Fatal outcomes have been reported.
Rare (≥ 0.01% and < 0.1%)	Hepatobiliary disorders	Hepatic failure[d]. Fatal outcomes have been reported.
	Skin and subcutaneous tissue disorders	Photosensitivity reaction

a. May be reduced by concomitant castration.
b. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
c. 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.
d. 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.
e. 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 was used in combination with LHRH agonists.

Increased PT/INR: Accounts of coumarin anticoagulants interacting with bicalutamide 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. Healthcare professionals are asked to report any suspected reactions https://nzphvc.otago.ac.nz/reporting/

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 is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, 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

BICALOX is a non-steroidal anti-androgen, 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 bicalutamide can result in antiandrogen withdrawal syndrome in a subset of patients.

BICALOX is a racemate with its antiandrogenic activity being almost exclusively in the R-enantiomer.

5.2. Pharmacokinetic properties

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

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 bicalutamide, 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 µg/mL are observed during daily administration of 50 mg doses of bicalutamide. At steady state the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.

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.

Bicalutamide is highly protein bound (racemate 96%, R-bicalutamide 99.6%) and extensively metabolised (oxidation and glucuronidation); its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

In a clinical study the mean concentration of R-bicalutamide in semen of men receiving 150 mg of bicalutamide was 4.9 µg/mL. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and equates to approximately 0.3 µg/kg. This is below that required to induce changes in offspring of laboratory animals.

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 and minor clinical pathology changes, are related to these activities. Enzyme induction and minor cardiac changes seen in dogs have not been observed in man. Atrophy of seminiferous tubules of the testes is a predicted class effect with anti-androgens 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 or 0.6 times human therapeutic concentrations at the recommended dose of 50 mg or 150 mg, respectively). No recovery was observed at 24 weeks after the completion of dosing in a 12-month rat study (at doses of approximately 2 or 0.9 times human concentrations at the recommended human dose of 50 mg or 150 mg, respectively). Following 12 months of repeated dosing in dogs (at doses of approximately 7 or 3 times human therapeutic concentrations at the recommended human dose of 50 mg or 150 mg, respectively), 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 or 0.6 times human therapeutic concentrations at the recommended human dose of 50 mg or 150 mg, respectively), 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, sodium starch glycollate, povidone, magnesium stearate, opadry white Y-1-7000.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 25°C. Protect from light and moisture.

6.5. Nature and contents of container

PVC/PVdC-Aluminium blisters: 28, 30, 56, 98 tablets.
HDPE bottle: 100, 500 tablets.

Not all pack types or sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

24 April 2008

10. DATE OF REVISION OF THE TEXT

27 December 2018

Summary table of changes

Section Changed	Summary of new information
All	SPC format
4.4, 4.5, 4.8	Additional information based on innovator data sheet, including coumarin and androgen deprivation therapy
4.6, 5.3	Additional information on fertility, as per innovator data sheet