NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Bicalaccord, 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 50 mg of Bicalutamide.

3. PHARMACEUTICAL FORM
Film-coated tablets

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of advanced prostate cancer in adult males aged 18 years and older 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

As combination therapy in Adult males including the elderly
One tablet (50 mg) once a day.

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

Children
BICALACCORD 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 WARNINGS AND PRECAUTIONS).

4.3 Contraindications
BICALACCORD is contraindicated in females and children.

BICALACCORD must not be given to any patient who has shown a hypersensitivity reaction to its use.

4.4 Special warnings and precautions for use
BICALACCORD is extensively metabolised in the liver. On the basis of currently available investigations, there may be slower excretion and accumulation of bicalutimide in instances of severe hepatic impairment. Caution is therefore required with patients with moderate to severe hepatic impairment. In these cases regular liver function tests (bilirubin, transaminases, alkaline phosphatase) must be carried out.

Severe hepatic changes and hepatic failure have been observed rarely with BICALACCORD (see ADVERSE EFFECTS). If there is clinical and/or biochemical evidence of severe hepatotoxicity, consideration should be given to discontinue BICALACCORD therapy.

4.5 Interaction with other medicines and other forms of interaction

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutmaide 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 *in vitro* studies have suggested the potential for bicalutamide to inhibit cytochrome 3A4, a number of clinical studies show the magnitude of any inhibition is unlikely to be of clinical significance.

In vitro studies have shown that bicalutamide can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is therefore recommended that if BICALACCORD is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

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

4.6 Fertility, pregnancy and lactation

BICALACCORD is contraindicated in females and must not be given to pregnant women or nursing mothers.

4.7 Effects on ability to drive and use machines

BICALACCORD is unlikely to impair the ability of patients to drive or operate machinery.

4.8 Undesirable effects

Bicalutamide in general, has been well tolerated with few withdrawals due to adverse events.

Post Marketing

Table 1 Frequency of Adverse Events

Frequency	**System Organ Class**	**Event**
Very common (≥10%)	Reproductive system and breast disorders General disorders	Breast tenderness[1], gynaecomastia[1] Hot flushes
Common (≥1% and <10%)	Gastrointestinal disorders Hepato-biliary disorders General disorders	Diarrhoea, nausea Hepatic changes (elevated levels of transaminases, jaundice)[2] Asthenia, pruritus
Uncommon (≥0.1% and <1%)	Immune system disorders Respiratory, thoracic and mediastinal disorders	Hypersensitivity reactions, including angioneurotic oedema and urticaria Interstitial lung disease
Rare (≥0.01% and <0.1%)	Gastrointestinal disorders Hepato-biliary disorders Skin and subcutaneous tissue disorders	Vomiting Hepatic failure Dry skin

[1.] May be reduced by concomitant castration.

[2.] Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see WARNINGS AND PRECAUTIONS).

Clinical Trials
In patients with advanced prostate cancer treated with Bicalutamide in combination with an GnRH analogue, the most frequent adverse experience was hot flushes (49%).

Diarrhoea was the adverse event most frequently leading to treatment withdrawal: 6% of the patients treated with flutamide-GnRH analogue and 0.5% of the patients treated with bicalutamide-GnRH analogue.

In the multicentre, double-blind, controlled clinical trial comparing bicalutamide 50 mg once daily with flutamide 250 mg three times a day, each in combination with a GnRH analogue, the following adverse experiences with an incidence of 5% or greater, regardless of causality, have been reported.

Incidence of Adverse Events

(≥5% in Either Treatment Group)

Regardless of Causality

Adverse Event	**Treatment Group Number of Patients (%)**	
	Bicalutamide Plus GnRH Analogue (n=401)	**Flutamide Plus GnRH Analogue (n=407)**
Body as a Whole		
Pain (General)	109 (27)	93 (23)
Back Pain	62 (15)	68 (17)
Asthenia	60 (15)	69 (17)
Pelvic Pain	52 (13)	46 (1)
Infection	41 (10)	35 (9)
Abdominal pain	33 (8)	31 (8)
Chest Pain	24 (6)	20 (5)
Headache	17 (4)	20 (5)
Flu Syndrome	16 (4)	20 (5)
Cardiovascular		

Hot Flushes	196 (49)	202 (50)
Hypertension	21 (5)	18 (4)
Digestive		
Constipation	67 (17)	50 (12)
Nausea	44 (11)	45 (11)
Diarrhoea	40 (10)	98 (24)
Increased Liver Enzyme Test+	25 (6)	40 (10)
Flatulence	22 (5)	6 (4)
Vomiting	12 (3)	20 (5)
Haemic and Lymphatic		
Anaemia #	29 (7)	35 (9)
Metabolic and Nutritional		
Peripheral Oedema	34 (8)	28 (7)
Hyperglycaemia	20 (5)	16 (4)
Weight Loss	16 (4)	20 (5)
Musculoskeletal		
Bone Pain	18 (4)	26 (6)
Nervous System		
Dizziness	30 (7)	27 (7)
Paraesthesia	24 (6)	27 (7)
Insomnia	19 (5)	30 (7)
Respiratory System		
Dypsnoea	30 (7)	24 (6)
Skin and Appendages		
Rash	25 (6)	20 (5)

Sweating	23 (6)	18 (4)
Urogenital		
Nocturia	35 (9)	43 (11)
Haematuria	30 (7)	20 (5)
Urinary Tract Infection	26 (6)	24 (6)
Impotence	20 (5)	29 (7)
Gynaecomastia	19 (5)	23 (6)
Urinary Incontinence	9 (2)	20 (5)

+ Increased liver enzymes tests, includes increased AST, ALT or both
# Anaemia includes anaemia, hypochromic and iron deficiency anaemia

Other less frequent (greater than or equal to 2%, but less than 5%) adverse experiences reported in the bicalutamide-GnRH analogue treatment group are listed below by body system and are in order of decreasing frequency within each body system regardless of causality. Some of these are commonly reported in elderly patients.

Body as a whole: Oedema, neoplasm, fever, neck pain, chills, sepsis.

Cardiovascular: Angina, pectoris, congestive heart failure.

Digestive: Anorexia, dyspepsia, rectal haemorrhage, dry mouth, melaena.

Endocrine: Breast pain.

Metabolic and Nutritional: Diabetes mellitus, alkaline phosphatase increased, weight gain, creatinine increased, dehydration, gout.

Musculoskeletal: Myasthenia, arthritis, myalgia, leg cramps, pathological fracture.

Nervous: Anxiety, depression, libido decreased, hypertonia, confusion, neuropathy, somnolence, nervousness.

Respiratory: Cough increased, pharyngitis, bronchitis, pneumonia, rhinitis, lung disorder.

Skin and Appendages: Dry skin, pruritus, alopecia, injection site reaction, hirsutism.

Urogenital: Urinary frequency, urination impaired, dysuria, urinary retention, urinary urgency.

Haematological: Anaemia.

Abnormal Laboratory Test Values: Laboratory abnormalities included elevated AST, ALT, bilirubin, BUN and creatinine and decreased haemoglobin and white cell count have been reported in both bicalutamide-GnRH analogue treated and flutamide-GnRH analogue treated patients. Increased liver enzyme tests and decreases in haemoglobin were reported less frequently in the bicalutamide plus GnRH analogue group. Other changes were reported with similar incidences in both treatment groups.

Hepatic changes (elevated levels of transaminases, jaundice) have been observed in clinical trials with bicalutamide. The changes were frequently transient, resolving or improving despite continued therapy or following cessation of therapy. The majority of the hepatic changes were seen within the first 6 months of bicalutamide therapy. Periodic liver function testing should be considered; particularly during the first 6 months of therapy and if patients have pre-existing hepatic abnormality. (see Warnings and Precautions).

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 BICALACCORD 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

Bicalutamide 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.

Bicalutamide 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 bicalutamide 150 mg 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. There are no preclinical findings that preclude the administration of bicalutamide to prostate cancer patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose monohydrate
- Sodium Starch Glycolate
- Povidone
- Magnesium Stearate
- Hypromellose
- Macrogol 400
- Titanium Dioxide

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

BICALACCORD 50 mg tablets, blister pack 28 tablets.

6.6 Special precautions for disposal

No special precautions for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

11th March 2010

10. DATE OF REVISION OF THE TEXT

5 April 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8.	Sponsor company name and address details updated