IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0915/015/001
Case No: 2070471

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Helsinn Birex Therapeutics Ltd

Damastown, **Mulhuddart**, **Dublin 15**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Bicalinn 50 mg film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **18/12/2009** until **11/09/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bicalinn 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg bicalutamide.
Also contains 60 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White, round, biconvex film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

4.2 Posology and method of administration

Adult males including the elderly: One tablet (50 mg) once a day. Treatment with Bicalinn should be started at the same time as treatment with an LHRH analogue or surgical castration.

Children: Bicalinn is contraindicated in children.

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 Special warnings and special precautions for use).

4.3 Contraindications

Bicalinn is contraindicated in females and children.

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

4.4 Special warnings and precautions for use

Initiation of treatment should be under the direct supervision of a specialist and subsequently patients should be kept under regular surveillance. Bicalinn 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 Bicalinn. Therefore, Bicalinn 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.

Severe hepatic changes and hepatic failure have been observed rarely with Bicalinn (see section 4.8 Undesirable effects). Bicalinn therapy should be discontinued if changes are severe.

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

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between Bicalinn 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 *in vitro* studies have suggested the potential for Bicalinn 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 Bicalinn can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is therefore recommended that if Bicalinn is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

4.6 Pregnancy and lactation

Bicalinn 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

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

4.8 Undesirable effects

Bicalinn 50 mg is only used in combination with surgical or medical castration. The reported adverse drug profile of Bicalinn 50 mg therefore includes effects that may also be seen with castration therapy alone. The most common reactions reported reflect the pharmacological activity; with the majority (53%) of patients reporting hot flushes and lower proportions (approximately 10%) reporting gynaecomastia or breast tenderness.

Table 1 Frequency of Adverse Reactions

Frequency	**System Organ Class**	**Event**
Very common (≥10%)	Reproductive system and breast disorders	Breast tenderness
		Gynaecomastia
	General disorders	Hot flushes
Common (≥1% and <10%)	Gastrointestinal disorders	Diarrhoea
		Nausea
	Hepato-biliary disorders	Hepatic changes (elevated levels of transaminases, jaundice)[1]
	General disorders	Asthenia
		Pruritus
Uncommon	Immune system disorders	Hypersensitivity reactions, including angioneurotic oedema and urticaria

(≥0.1% and <1%)		
	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease
Rare	Gastrointestinal disorders	Vomiting
(≥0.01% and <0.1%)		
	Hepato-biliary disorders	Hepatic failure
	Skin and subcutaneous tissue disorders	Dry skin

Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4 Special warnings and special precautions for use). Periodic liver function testing should be considered.

In addition, the following adverse experiences were reported in clinical trials (as possible adverse drug reactions in the opinion of investigating clinicians, with a frequency of ≥1%) during treatment with Bicalinn plus an LHRH analogue. No causal relationship of these experiences to drug treatment has been made and some of the experiences reported are those that commonly occur in elderly patients:

Cardiovascular system:	heart failure
Gastrointestinal system:	anorexia, dry mouth, dyspepsia, constipation, flatulence
Central nervous system:	dizziness, insomnia, somnolence, decreased libido
Respiratory system:	dyspnoea
Urogenital:	impotence, nocturia
Haematological:	anaemia
Skin and appendages:	alopecia, rash, sweating, hirsutism
Metabolic and nutritional:	diabetes mellitus, hyperglycaemia, oedema, weight gain, weight loss
Whole body:	abdominal pain, chest pain, headache, pain, pelvic pain, chills

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 Bicalinn 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

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

5.2 Pharmacokinetic properties

Bicalinn 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 Bicalinn, 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 Bicalinn. 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.
Bicalinn is highly protein bound (racemate 96%, R-bicalutamide 99.6%) and extensively metabolised via 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 Bicalinn 150 mg was 4.9 microgram/ml. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and equates to approximately 0.3 microgram/kg. This is below that required to induce changes in offspring of laboratory animals.

5.3 Preclinical safety data

Bicalinn is a potent antiandrogen. Expected pharmacological effects of antiandrogens seen in animal studies include the following: atrophy of the prostate and seminal vesicles, benign Leydig cell tumours (rats) and adrenal cortical hypertrophy. Bicalinn is a mixed function oxidase inducer in animals and thyroid hypertrophy and adenoma (rat) and hepatocellular carcinoma (male mice) are a consequence of this. Enzyme induction has not been observed in man. None of the findings in preclinical testing are considered to have relevance to the treatment of advanced prostate cancer patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Lactose Monohydrate
Povidone K-30
Sodium Starch Glycollate (Type A)
Magnesium Stearate

Film-coating:

Opadry White Y-1-7000 containing:
Hypromellose
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC /aluminium blister packs of 28 tablets.

Available in pack sizes: 10, 14, 28,50,60,90,100 Film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Helsinn Birex Therapeutics Limited
Damastown
Mulhuddart
Dublin 15

8 MARKETING AUTHORISATION NUMBER

PA0915/015/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 12th September 2008

10 DATE OF REVISION OF THE TEXT

December 2009