Bi ELIGARD® cp
BICALUTAMIDE-LEUPRORELIN COMBINATION THERAPY

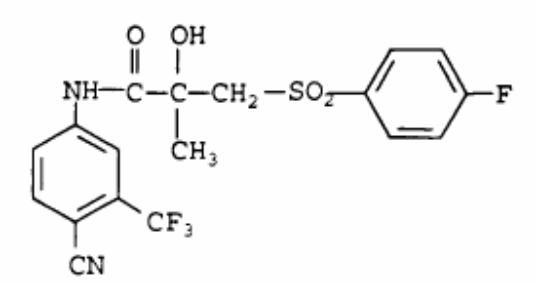
NAME OF THE MEDICINE

Bi ELIGARD® cp combination therapy is the brand name for composite packs containing Eligard® (leuprorelin acetate) subcutaneous depot plus Bicalutamide Tolmar 50 mg tablets.

Tablets: Bicalutamide

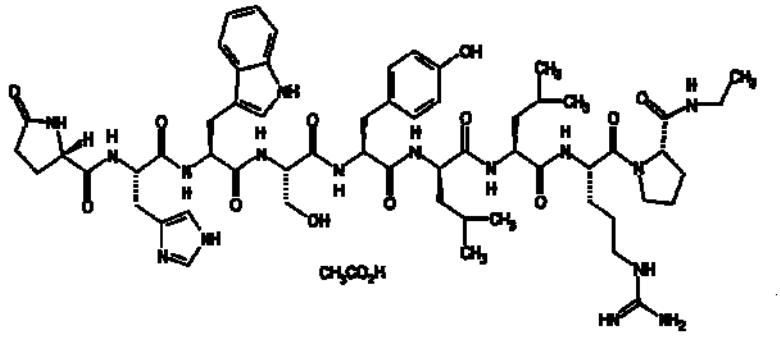
Modified release injection: Leuprorelin acetate

Bicalutamide



Chemical name: (*RS*)-4'-Cyano-α', α', α',-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide
Molecular formula: $C_{18}H_{14}F_4N_2O_4S$
Molecular weight: 430.38 g/mol
CAS registry number: 90357-06-5

Leuprorelin acetate



Chemical name: 5-oxo-L-prolyl-L-histidyl- L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)
Molecular formula: $C_{59}H_{84}N_{16}O_{12}\cdot C_2H_4O_2$
Molecular weight: 1269.45 g/mol
CAS registry number: 74381-53-6

DESCRIPTION

Bicalutamide

Bicalutamide is a fine white to off-white powder. At 37°C it is practically insoluble in water (4.6 mg/litre), acid (4.6 mg/litre at pH 1) and alkali (3.7 mg/litre at pH 8). In organic solvents it is slightly soluble in ethanol, sparingly soluble in methanol and freely soluble in acetone and tetrahydrofuran.

Bicalutamide Tolmar tablets are white film-coated tablets containing 50 mg bicalutamide. Each tablet contains the following excipients: lactose monohydrate, sodium starch glycollate type A, povidone, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

Leuprorelin

Eligard® is a sterile polymeric matrix formulation of leuprorelin acetate for subcutaneous injection. It is designed to deliver leuprorelin acetate at a controlled rate over a therapeutic period.

Leuprorelin acetate is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular steroidogenesis. The analogue possesses greater potency than the natural hormone.

Leuprorelin acetate is a white to near white powder, freely soluble in water and glacial acetic acid.

Eligard® Composition

Eligard® is available in a single use kit. The kit consists of a two-syringe mixing system, a 20-gauge 5/8 inch needle (for Eligard® 1 month and Eligard® 3 month), a silicone desiccant pouch to control moisture uptake, and package insert for constitution and administration procedures. Each syringe is individually packaged. One contains the Atrigel® Delivery System and the other contains leuprorelin acetate.

Eligard® is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. Eligard® is administered subcutaneously where it forms a solid drug delivery depot.

The Atrigel® Delivery System is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable polyglactin. The polymer is dissolved in a biocompatible solvent, *N*-methyl-2-pyrrolidone. The polyglactin mixture and volume differ with each presentation of Eligard®.

Eligard® contains no anti-microbial agent. Eligard® does not contain: lactose, sucrose, gluten, tartrazine, or any other azo dyes.

Eligard® 1 month contains 10.6 mg of lyophilised leuprorelin acetate. Eligard® 1 month

delivers 7.5 mg of leuprorelin acetate (equivalent to approximately 7.0 mg leuprorelin free base) dissolved in 160 mg *N*-methyl-2-pyrrolidone and 82.5 mg polyglactin. The approximate weight of the administered formulation is 250 mg. It is designed to deliver 7.5 mg of leuprorelin acetate at a controlled rate over a 1 month therapeutic period.

Eligard® 3 month contains 29.2 mg lyophilised leuprorelin acetate. Eligard® 3 month delivers 22.5 mg of leuprorelin acetate (equivalent to approximately 21 mg leuprorelin free base) dissolved in 193.9 mg *N*-methyl-2-pyrrolidone and 158.6 mg polyglactin. The approximate weight of the administered formulation is 375 mg. It is designed to deliver 22.5 mg of leuprorelin acetate at a controlled rate over a 3 month therapeutic period.

PHARMACOLOGY

Bicalutamide

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. This inhibition impairs the growth and encourages apoptosis in androgen- dependent tumour cells and regression of prostatic tumours. In a subset of patients who experience disease progression while receiving bicalutamide, discontinuation of the medicine may result in an 'anti-androgen withdrawal syndrome', which manifests as a fall in prostate specific antigen (PSA) level. It is unknown whether this phenomenon translates to a prolongation of tumour response or survival.

Bicalutamide is a racemate with its anti-androgenic activity being almost exclusively in the (R)-enantiomer.

Pharmacokinetics

Absorption

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

Distribution

Bicalutamide is highly protein bound (racemate 96%, R-enantiomer 99.6%).

Steady state plasma concentrations of the (R)-enantiomer of approximately 9 µg per mL are observed during daily administration of bicalutamide 50 mg. At steady state the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.

Metabolism and Elimination

Bicalutamide undergoes stereospecific metabolism. Bicalutamide is extensively metabolised (via oxidation and glucuronidation). Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

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.

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.

Leuprorelin

Leuprorelin acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Animal and human studies indicate that after an initial stimulation, chronic administration of leuprorelin acetate results in suppression of testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy.

Administration of leuprorelin acetate has resulted in inhibition of the growth of certain hormone-dependent tumours (prostatic tumours in Noble and Dunning male rats and DMBA-induced mammary tumours in female rats) as well as atrophy of the reproductive organs.

In humans, administration of leuprorelin acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and oestrone and oestradiol in premenopausal females). However, continuous administration of leuprorelin acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate threshold (≤ 50 ng/dL). These decreases occur within two to six weeks after initiation of treatment.

Leuprorelin acetate is not active when given orally.

Pharmacokinetics

Absorption

The absorption pharmacokinetic parameters determined for Eligard® are presented in Table 1.

Table 1. Absorption pharmacokinetic parameters for Eligard®

Presentation of Eligard®	Cmax ± SD(ng/mL)	Tmax ± SD (hours)
1 month	25.3 ± 11.3	4.7 ± 1.4
3 month *	127 ± 39	4.6 ± 1.6
3 month**	107 ± 50	4.5 ± 1.5

* first dose

** second dose

After the initial increase following each injection, mean serum concentrations remained relatively constant; 0.28 – 2.0 ng/mL for Eligard® 1 month, 0.2 – 2.0 ng/mL for Eligard® 3 month. There was no evidence of significant accumulation during repeated dosing. Non-detectable leuprorelin serum concentrations have been observed during chronic Eligard® administration, but testosterone levels were maintained at castrate levels.

Distribution

The mean steady-state volume of distribution of leuprorelin following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins

ranged from 43% to 49%.

Metabolism
In healthy male volunteers, a 1 mg bolus of leuprorelin administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

Drug metabolism studies were not conducted with Eligard®. Upon administration with different leuprorelin acetate formulations, the major metabolite of leuprorelin acetate is a pentapeptide (M-1) metabolite.

Excretion
Drug excretion studies were not conducted with Eligard®.

Special Populations
Geriatrics
The majority of the patients (approximately 70%) studied in these clinical trials were age 70 and older.

Paediatrics
The safety and effectiveness of Eligard® in paediatric patients have not been established (see CONTRAINDICATIONS).

Renal and Hepatic Insufficiency
The pharmacokinetics of Eligard® in hepatically and renally impaired patients have not been determined.

CLINICAL TRIALS

Combination therapy (with medical castration) in advanced prostate cancer
In a large multicentre, controlled clinical trial, 813 patients with previously untreated advanced prostate cancer were randomized to receive bicalutamide 50 mg once daily (404 patients) or flutamide 250 mg (409 patients) three times a day, each in combination with a Luteinising Hormone Releasing Hormone Agonist (LHRH Agonist) (either goserelin acetate implant or leuprorelin acetate depot). At the time of analysis, the median time of follow-up was 49 weeks. Bicalutamide/ LHRH agonist therapy was associated with a statistically significant ($p = 0.005$) improvement in time to treatment failure.

Subjective responses, (including scores for pain, analgesic use and Eastern Oncology Cooperative Group (ECOG) performance status) assessed in patients with symptoms at entry were seen in 95 (52%) patients treated with bicalutamide and in 88 (54%) patients treated with flutamide, each in combination therapy with LHRH agonists. This small difference was not statistically significant between bicalutamide 50 mg combination therapy and flutamide combination therapy.

Meta-Analysis

There is considerable debate regarding the relative merits of combination versus monotherapy in advanced prostate cancer, summarised by Dalesio et al 1995[1] in their meta-analysis of trials of maximal androgen blockade (MAB). This analysis showed no statistically significant reduction in the annual odds of death in favour of MAB. The meta-analysis included the effect of MAB only on mortality, and did not measure other end-points such as time to disease progression.

INDICATIONS

Bicalutamide

Treatment of advanced prostate cancer in combination with LHRH agonist therapy.

Leuprorelin

Eligard® is indicated for the palliative treatment of advanced prostate cancer.

CONTRAINDICATIONS

Bicalutamide

Bicalutamide is contraindicated in females and children.

Known hypersensitivity to bicalutamide or any other constituents of the formulation.

Co-administration of terfenadine, astemizole or cisapride with bicalutamide is contraindicated (see INTERACTIONS WITH OTHER MEDICINES).

Leuprorelin

Eligard® is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogues or any of the components of Eligard®. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogues have been reported in the literature.

Eligard® is contraindicated in women who are breastfeeding, pregnant or intending to become pregnant and in paediatric patients. Eligard® was not studied in women or children. Moreover, leuprorelin acetate can cause foetal harm when administered to a pregnant woman. Major foetal abnormalities were observed in rabbits but not in rats after administration of leuprorelin acetate throughout gestation. There were increased foetal mortality and decreased foetal weights in rats and rabbits. The effects on foetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. The possibility exists that spontaneous abortion may occur.

Eligard® is contraindicated in patients who previously underwent orchiectomy (as with other

[1] *Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. Lancet 1995; 346: 265-269.*

GnRH agonists, Eligard® does not result in further decrease of serum testosterone in case of surgical castration). Eligard® is contraindicated as a sole treatment in prostate cancer patients with spinal cord compression or evidence of spinal metastases.

PRECAUTIONS

Bicalutamide

In patients with metastatic prostate cancer, treatment with bicalutamide monotherapy has been associated with reduced survival compared to castration. Bicalutamide should therefore not be used without concomitant LHRH agonist therapy in these patients.

Bicalutamide 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 bicalutamide. Therefore, bicalutamide 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 these changes occur within the first 6 months of bicalutamide therapy.

Rare cases of death or hospitalisation due to severe liver injury have been observed with bicalutamide (see ADVERSE EFFECTS). Bicalutamide therapy should be discontinued if at any time a patient develops jaundice or if serum ALT rises above two times the upper limit of normal.

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 bicalutamide in combination with LHRH agonists.

Potentiation of coumarin anticoagulant effects have been reported in patients receiving concomitant bicalutamide 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 INTERACTIONS WITH OTHER MEDICINES and ADVERSE EFFECTS).

QT/QTc interval prolongation

Androgen deprivation therapy may prolong QT/QTc interval. Prescribers should consider whether the benefits of androgen deprivation therapy outweight the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities and in patients taking drugs known to prolong the QT interval. Electrolyte imbalances should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

Effects on Fertility

Administration of bicalutamide may lead to inhibition of spermatogenesis. The long-term effects of bicalutamide on male fertility have not been studied. In male rats dosed at 250

mg/kg/day (less than human therapeutic concentrations after the maximum recommended clinical dose of 150 mg), the precoital interval and time to successful mating were increased in the first pairing but no effects on fertility following successful mating were seen. These effects were reversed by 7 weeks after the end of an 11-week period of dosing. A period of subfertility or infertility should be assumed in man.

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 bicalutamide, patients and/or their partners should follow adequate contraception during bicalutamide therapy and for 130 days after bicalutamide therapy.

Use in Pregnancy (Category D)[2]

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

Use in Lactation

Bicalutamide is contraindicated in females and must not be given to breast-feeding mothers.

Genotoxicity

Bicalutamide was inactive in *in vitro* tests for gene mutation and in *in vitro* and *in vivo* tests for clastogenicity.

Carcinogenicity

Two-year oral carcinogenicity studies were conducted in male and female rats and mice at doses of 5, 15 or 75 mg/kg/day of bicalutamide. A variety of tumour target organ effects were identified and were attributed to the antiandrogenicity of bicalutamide, namely, testicular benign interstitial (Leydig) cell tumours in male rats at all dose levels and uterine adenocarcinoma in female rats at 75 mg/kg/day (at these dose levels plasma (R)-bicalutamide concentrations were less than human therapeutic concentrations after the maximum recommended clinical dose of 150 mg). There is no evidence of Leydig cell hyperplasia patients; uterine tumours are not relevant to the indicated patient population.

A small increase in the incidence of hepatocellular carcinoma in male mice given 75 mg/kg/day of bicalutamide (approximately 2 times human therapeutic concentrations after the maximum recommended clinical dose of 150 mg) and an increased incidence of benign thyroid follicular cell adenomas in rats given 5 mg/kg/day (less than the human therapeutic concentrations after the maximum recommended clinical dose of 150 mg) and above were recorded. These neoplastic changes were progressions of non-neoplastic changes related to hepatic enzyme induction observed in animal toxicity studies. Enzyme induction has not been observed following bicalutamide administration in man.

[2] *Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*

Effects on ability to drive and use machines

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

Leuprorelin

Eligard®, like other LH-RH agonists, causes a transient increase in serum concentrations of testosterone during the first week of treatment. Patients may experience worsening of symptoms or onset of new signs and symptoms during the first few weeks of treatment, including bone pain, neuropathy, haematuria, or bladder outlet obstruction. Isolated cases of ureteral obstruction and/or spinal cord compression, which may contribute to paralysis with or without fatal complications, have been observed in the palliative treatment of advanced prostate cancer using LH-RH agonists.

Initiating therapy with a non-steroidal anti-androgen at the same time as leuprorelin acetate therapy has proven benefit in reducing flare reactions in 'at risk' patients (e.g. those with thecal indentation, or at risk of cord compression, and patients with bladder neck obstruction).

Additional administration of an appropriate antiandrogen should be considered beginning 3 days prior to leuprorelin therapy and continuing for the first two to three weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone.

If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

Long-term administration of leuprorelin will cause suppression of pituitary gonadotropins and gonadal hormone production with clinical symptoms of hypogonadism. These changes have been observed to reverse on discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

General

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.

Response to Eligard® should be monitored by measuring serum concentrations of testosterone and prostate-specific antigen periodically.

Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

Following surgical castration, Eligard® does not lead to a further decrease in serum testosterone levels in male patients. A proportion of patients will have tumors which are not sensitive to hormone manipulation. This is termed castrate-resistant prostate cancer. Signs and/or symptoms of tumor progression despite adequate testosterone suppression are diagnostic of this condition. Current treatment paradigms recommend continued GnRH therapy along with other therapeutic regimes for this circumstance.

Hyperglycemia and Diabetes

Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes.

Cardiovascular Diseases

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

Effect on QT/QTc Interval

Androgen deprivation therapy may prolong the QT interval. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

Changes in Bone Density

Bone loss can be expected as part of natural aging and can also be anticipated during the hypo-androgenic state caused by long-term use of leuprorelin acetate. In patients with significant risk factors for decreased bone mineral content and/or bone mass such as family history of osteoporosis, chronic use of corticosteroids or anticonvulsants or chronic abuse of alcohol or tobacco, leuprorelin acetate may pose additional risk. In these patients, risk versus benefit must be weighed carefully before initiation of leuprorelin acetate therapy.

Convulsions

Post marketing reports of convulsions have been observed in patients on leuprorelin acetate therapy with or without a history of predisposing factors. These included patients in the female and paediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumours, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above. Convulsions are to be managed according to the current clinical practice.

Effects on fertility

Preclinical studies with leuprorelin acetate in rats demonstrated reversible, expected effects (given that leuprorelin acetate has known pharmacological effects on reproductive endocrinology) on the reproductive system of both sexes.

Leuprorelin acetate did not show teratogenicity in rats.

Clinical and pharmacological studies in adults with leuprorelin acetate and similar analogues have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

Use in pregnancy (Category D) [2]

(see CONTRAINDICATIONS).

Although not relevant to the approved indication, leuprorelin acetate is contraindicated in pregnancy due to its embryotoxic effects.

Use in lactation

Eligard® is contraindicated for use in breastfeeding women.

Paediatric Use

Eligard® is contraindicated in paediatric patients. It has not been studied in this population.

Use in the Elderly

The majority of the patients (approximately 70%) studied in the clinical trials were age 70 and older.

Hepatic and Renal Insufficiency

Eligard® was not studied in hepatically and renally impaired patients.

Genotoxicity

Mutagenicity studies have been performed with leuprorelin acetate using bacterial and mammalian systems and with Eligard® 1 month in bacterial systems. These studies provided no evidence of a genotoxic potential.

Carcinogenicity

Two-year carcinogenicity studies were conducted with leuprorelin acetate in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprorelin acetate-induced tumours or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprorelin acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Effects on laboratory tests

In the majority of non-orchiectomised patients, testosterone levels increased during the first week of treatment. They then decreased and by day 14 had returned to baseline levels or below. Castrate levels were reached in 2 to 4 weeks. Once achieved, castrate levels were maintained as long as the patient received their injections. Transient increases in acid phosphatase levels may occur early in the treatment period; however, by the fourth week the elevated levels usually decreased to values at or near normal. Therapy with leuprorelin results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal

functions conducted during and after leuprorelin therapy may be affected.

Effects on ability to drive and use machines

No studies on the effects of Eligard® on the ability to drive and use machines have been performed. The ability to drive and operate machines may be impaired due to fatigue, dizziness and visual disturbances being possible side effects of treatment or resulting from the underlying disease.

INTERACTIONS WITH OTHER MEDICINES

Bicalutamide

Bicalutamide is extensively metabolised (via oxidation and glucuronidation) in the liver. Bicalutamide has shown no evidence of causing enzyme induction in humans during dosing at 50 mg daily in man. *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.

The clinically or potentially significant medicine interactions between bicalutamide and the following agents/medicine classes, which are theoretical or have been observed, are described below. The medicine/medicine interactions described include both interactions mediated through effects on P450 metabolism and interactions mediated through other mechanisms.

Effects of bicalutamide on other medicines

LHRH agonists: Although there is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide 50 mg 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.

Cytochrome P450: Bicalutamide is an inhibitor of CYP 3A4 and has been shown to increase plasma levels of midazolam by up to 80 %. Therefore, concomitant use of terfenadine, astemizole and cisapride is contraindicated. Caution should be exercised with other medicines metabolised by CYP 3A4, such as cyclosporin, calcium channel blockers, HIV antivirals, HMGCoA reductase inhibitors, carbamazepine, quinidine etc.

Demonstrated interactions

Warfarin: *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 administered in patients who are already receiving coumarin anticoagulants, PT/INR should be closely monitored and adjustments of anticoagulant dose considered (see PRECAUTIONS and ADVERSE EFFECTS).

Theoretical interactions

Caution should be exercised when prescribing bicalutamide with other medicines which may inhibit medicine oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of bicalutamide and an increase in adverse effects.

Leuprorelin

There are no reports of drug interactions with leuprorelin acetate to date.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Eligard® 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) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see PRECAUTIONS).

ADVERSE EFFECTS

Bicalutamide

Bicalutamide 50 mg in general, has been well tolerated with few withdrawals due to adverse events.

Clinical trial data-Combination therapy (with medical castration) in advanced prostate cancer

The following adverse experiences were reported in clinical trials (as possible adverse medicine effects in the opinion of investigating clinicians, with a frequency of ≥ 1%) during treatment with bicalutamide 50 mg plus an LHRH agonist. No causal relationship of these experiences to medicine treatment has been made and some of the experiences reported are those that commonly occur in elderly patients.

Table 2: Bicalutamide adverse drug effects by frequency and System Organ Class

Frequency	System Organ Class	Event
Very Common (≥10%)	*Blood and lymphatic*	anaemia
	Nervous system disorders	dizziness
	Vascular disorder	hot flush
	Gastrointestinal disorders	abdominal pain, constipation, nausea
	Renal and urinary disorders	haematuria
	Reproductive system and breast disorders	breast tenderness[1], gynaecomastia[1]
	General disorders and administration site conditions	asthenia, chest pain, oedema

Frequency	System Organ Class	Event
Common (≥1%-<10%)	*Metabolism and nutrition disorders*	Decreased appetite (anorexia)
	Psychiatric disorders Nervous	decreased libido, depression
	system disorders	somnolence
	Gastrointestinal disorders	dyspepsia, flatulence
	Hepato-biliary disorders	hepatotoxicity, jaundice, hypertransaminasaemia[2]
	Cardiac disorders	myocardial Infarction (fatal outcomes have been reported)[3], cardiac failure[3]
	Skin and subcutaneous tissue disorders	alopecia, hirsutism/ hair re-growth, rash, dry skin, pruritis
	Reproductive system and breast disorders	erectile dysfunction
	Investigations	weight increased
Uncommon (≥0.1%-<1%)	*Immune system disorders*	hypersensitivity reactions angiodema and urticaria
	Respiratory, thoracic and mediastinal disorders	interstitial lung disease (ILD)[4] - fatal outcomes have been reported.
Rare (≥0.01%-<0.1%)	*Hepato-biliary disorders*	hepatic failure[5]- fatal outcomes have been reported.
	Skin and subcutaneous tissue disorders	photosensitivity reaction

[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

[3]Observed in a pharmaco-epidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risk appears to be increased when bicalutamide tablets 50 mg was used in combination with LHRH agonists but no increase in risk was evident when bicalutamide tablets 150 mg was used as a monotherapy to treat prostate cancer.

[4]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

[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 hepatic failure in patients receiving treatment in the open-label bicalutamide arm of the 150 mg EPC studies

Increased PT/INR

Accounts of coumarin anticoagulants interacting with bicalutamide have been reported in post marketing surveillance (see INTERACTIONS WITH OTHER MEDICINES and PRECAUTIONS).

Leuprorelin

Eligard®, like other LH-RH analogues, caused a transient increase in serum testosterone concentrations during the first two weeks of treatment. Therefore, potential exacerbations of signs and symptoms of the disease during the first few weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or haematuria. If these conditions are aggravated, it may lead to neurological problems such as weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms (see PRECAUTIONS).

'Flare' Phenomenon: The initial increase in circulating levels of pituitary gonadotropins and gonadal steroids leads in some patients to a transient exacerbation of symptoms and signs ('flare' phenomenon). The exacerbation may include worsened bone pain, ureteric obstruction and spinal cord compression. This possibility should be taken into account in deciding to initiate leuprorelin acetate therapy in patients with existing obstructive uropathy or vertebral metastases. Early symptoms of spinal cord compression such as paraesthesia should alert the physician to the need for intensive monitoring and possible treatment.

There is no information available on the clinical effects of interrupting leuprorelin acetate therapy and whether this will produce a withdrawal 'flare'.

Initiating therapy with a non-steroidal anti-androgen at the same time as leuprorelin acetate therapy has proven benefit in reducing flare reactions in 'at risk' patients.

The safety of Eligard® was evaluated in open-label, multicentre studies. In Eligard® clinical studies conducted, patient injection sites were closely monitored. The adverse reactions from injections sites are summarised in Table 3.

Table 3. Summary of adverse reactions from Eligard® injection sites

Presentation	Eligard® 1 month	Eligard® 3 month
Total number of injections (N=)	716	230
Adverse reactions (% of injections)		
Transient burning/stinging	34.6	21.7
Pain	4.3	3.5
Erythema	2.6	0.9
Mild bruising	2.5	1.7
Pruritis	1.4	0.4
Induration	0.4	–
Ulceration	0.1	–

The majority (84%) of transient burning/stinging events for Eligard® 1 month were reported as mild. Pain was generally reported as brief in duration and mild in intensity. Erythema were

all reported as mild and generally resolved within a few days post-injection.

The majority (86%) of transient burning/stinging events for Eligard® 3 month were reported as mild. Pain was generally reported as brief in duration and mild in intensity. One of the reports characterized the erythema as mild and resolved within 7 days. The other was moderate and resolved within 15 days. Neither patient experienced erythema at multiple injections.

The following possibly or probably related systemic adverse events occurred during clinical trials of up to six months of treatment with Eligard® 1 month and Eligard® 3 month, and were reported in ≥ 2% and < 2% of patients (Tables 4 and 5, respectively). Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related were excluded.

More Common Reactions (incidence ≥ 2%)

Table 4. Incidence (%) of Possibly or Probably Related Systemic Adverse Events Reported by ≥ 2% of Patients Treated with Eligard® 1 month and Eligard® 3 month for up to six months

	Adverse Event	Eligard® 1 month [1] N (%)	Eligard® 3 month [2] N (%)
Body as a Whole	Malaise and Fatigue*	21 (17.5%)	7 (6.0 %)
	Weakness		
	Dizziness	4 (3.3%)	–
Cardiovascular	Hot flashes/sweats*	68 (56.7%)	66 (56.4%)
Genitourinary	Atrophy of Testes *	6 (5.0%)	-
	Nocturia	-	–
	Urinary frequency	-	3 (2.6 %)
Digestive	Gastroenteritis/ Colitis	3 (2.5%)	-
	Nausea	-	4 (3.4 %)
Reproductive	Gynaecomastia *	-	-
	Testicular pain	-	-
Skin	Clamminess *	-	–
	Night sweats *	-	–
	Alopecia	-	–
	Pruritis	-	3 (2.6 %)
Psychiatric	Decreased libido *	-	–
Musculoskeletal	Myalgia	-	–
	Arthralgia	-	4 (3.4 %)
	Pain in limb		

1. adverse events are classified using ICD–9 terms

2. adverse events are classified using MedDRA terms

* Expected pharmacological consequences of testosterone suppression.

Less Common Reactions (incidence < 2%)

Table 5. Possibly or Probably Related Systemic Adverse Events Reported by < 2% of Patients Treated with Eligard® 1 month[1] and Eligard® 3 month[2] for up to six months

Body System	Adverse Event
General	Sweating*, insomnia, syncope, rigors, weakness, lethargy
Gastrointestinal	Flatulence, constipation, dyspepsia
Haematologic	Decreased red blood cell count, haematocrit and haemoglobin
Metabolic	Weight gain
Musculoskeletal	Tremor, backache, joint pain, muscle atrophy, limb pain
Nervous	Disturbance of smell and taste, depression, vertigo
Psychiatric	Insomnia, depression, loss of libido*
Skin	Alopecia, clamminess, night sweats*, sweating increased*
Urogenital / Reproductive	Decreased libido*, gynaecomastia*, breast tenderness*, testicular atrophy*, testicular pain, erectile dysfunction*, penis disorder*, reduced penile size*
Renal and urinary disorders	Difficulties with urination, pain on urination, scanty urination, bladder spasm, blood in urine and urinary retention, urinary urgency, incontinence, nocturia, urinary tract infection
Vascular	Hypertension, hypotension

1. adverse events are classified using ICD–9 terms
2. adverse events are classified using MedDRA terms

* Expected pharmacological consequence of testosterone suppression.

Post-marketing experiences

Pituitary Apoplexy

During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin releasing hormone agonists, with a majority occurring within two weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as a sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Other Adverse Effects

During post-market surveillance with LH-RH agonists; diabetes mellitus, myocardial infarction, cerebrovascular accident and sudden cardiac death have also been reported (see PRECAUTIONS).

Anaphylactic/anaphylactoid reactions have been reported after GnRH agonist analog administration.

Postmarketing reports of convulsions have been observed in patients on leuprorelin acetate with or without a history of predisposing factors. Convulsions are to be managed according to the current clinical practice.

Muscular atrophy has been observed with long term use of products in this class.

DOSAGE AND ADMINISTRATION

Bicalutamide

ADULT MALES INCLUDING THE ELDERLY

One tablet (50 mg) once a day.

Treatment with bicalutamide 50 mg should be started at the same time as treatment with a LHRH agonist.

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 PRECAUTIONS). In such cases, a lower or less frequent dose may be considered.

Leuprorelin

IMPORTANT: Allow the product to reach room temperature before using**. Once mixed, Eligard® must be administered within 30 minutes**. Discard the constituted product if not administered within 30 minutes.

The two syringes are coupled and the product is mixed by transferring the contents from syringe to syringe immediately before administration to the patient. Refer to the enclosed leaflet titled Eligard® Mixing Procedure in the Eligard® carton for the full MIXING INSTRUCTIONS. The syringes are uncoupled and the needle is attached prior to injection. The product is injected subcutaneously into areas with adequate amounts of subcutaneous tissue (such as the abdomen) and that do not have excessive pigment, nodules, lesions, or hair. As with other drugs administered by subcutaneous injection, the injection site should be varied periodically.

When thoroughly mixed, the suspension will appear a light tan to tan colour (Eligard® 1 month) or a colourless to pale yellow colour (Eligard® 3 month). The mixed solution colour is not representative of product quality. An occasional slightly grey appearance of the mixed solution may be due to tiny air bubbles and will not affect the product quality.

Eligard® should not be injected in the arm.

The recommended dose of Eligard® 1 month is one injection every month.
The recommended dose of Eligard® 3 month is one injection every three months.

Eligard® 1 and 3 month presentations have different release characteristics and therefore, fractional, multiple and/or combinational doses are not equivalent to each other and should not be given.

Eligard® contains no antimicrobial agent and is for single use in one patient only. Discard any residue.

The injection delivers leuprorelin acetate, incorporated in a polymer formulation. It is administered subcutaneously and provides continuous release of leuprorelin for one month for Eligard® 1 month, three months for Eligard® 3 month.

OVERDOSAGE

Bicalutamide

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.

Leuprorelin

In clinical trials using daily subcutaneous leuprorelin acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

There is no clinical experience with the effects of an acute overdose. Because the acute animal toxicity of the drug is low, adverse effects are not expected. In the event of an overdose the patient should be monitored and supportive treatment given, if considered necessary.

For information on the management of overdose, contact the Poisons Information Centre for advice on 13 11 26 (Australia) or 0800 764 766 (New Zealand).

PRESENTATION AND STORAGE CONDITIONS

Bi ELIGARD cp® 1 month consisting of **Eligard® 1 month** (available in a single use kit that delivers 7.5 mg leuprorelin acetate. The Eligard® 1 Month drug product consists of a two-syringe mixing system, a sterile 20-gauge, 5/8-inch needle, and silica gel desiccant to control moisture uptake. Syringe B, made of cyclic olefin copolymer and sealed with a chlorobutyl closure, contains aseptically filled, lyophilized leuprorelin acetate. Syringe A, constructed of polypropylene and sealed with a polypropylene or polyethylene cap, contains the Atrigel® Delivery System.) and 28 **Bicalutamide Tolmar 50 mg film coated tablets (**a white to off-white, round, film-coated, biconvex tablet, engraved with 'BC 50' on one face and plain on the other) **(AUST R 237653)**

Bi ELIGARD cp® 3 month consisting of **Eligard® 3 month** (available in a single use kit that delivers 22.5 mg leuprorelin acetate. The Eligard® 3 Month drug product consists of a two-syringe mixing system, a sterile 20-gauge, 5/8-inch needle, and silica gel desiccant to control moisture uptake. Syringe B, made of cyclic olefin copolymer and sealed with a chlorobutyl closure, contains aseptically filled, lyophilized leuprorelin acetate. Syringe A, constructed of polypropylene and sealed with a polypropylene or polyethylene cap, contains the Atrigel® Delivery System) and 28 **Bicalutamide Tolmar 50 mg film coated tablets (**a white to off-white, round, film-coated,

biconvex tablet, engraved with 'BC 50' on one face and plain on the other) **(AUST R 238311)**

Bi ELIGARD cp® 3 month consisting of Eligard® 3 month (available in a single use kit that delivers 22.5 mg leuprorelin acetate. The Eligard® 3 Month drug product consists of a two-syringe mixing system, a sterile 20-gauge, 5/8-inch needle, and silica gel desiccant to control moisture uptake. Syringe B, made of cyclic olefin copolymer and sealed with a chlorobutyl closure, contains aseptically filled, lyophilized leuprorelin acetate. Syringe A, constructed of polypropylene and sealed with a polypropylene or polyethylene cap, contains the Atrigel® Delivery System) and 84 **Bicalutamide Tolmar 50 mg film coated tablets** (a white to off-white, round, film-coated, biconvex tablet, engraved with 'BC 50' on one face and plain on the other). **(AUST R 237652)**

Bi ELIGARD cp® should be stored between 2-8°C (refrigerate).

Individual components

Eligard® should be stored below 8°C (refrigerate).

The patient may store Eligard® below 25°C in intact packaging for a period of 8 weeks prior to administration.

Bicalutamide Tolmar 50mg film coated tablets are supplied in PVC/PVDC/Al blister packs and may be stored below 30ºC when protected from moisture and light.

NAME AND ADDRESS OF THE SPONSOR

Tolmar Australia Pty Ltd,
Pymble,
Sydney NSW 2073
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

24 May 2016

DATE OF MOST RECENT AMENDMENT

22 September 2017