▼This medicinal product is subject to additional monitoring in Australia due to approval of an extension of indications. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
DIPHERELINE
triptorelin (as embonate) 3.75 mg, 11.25 mg & 22.5 mg
powder for suspension

1 NAME OF THE MEDICINE

triptorelin embonate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diphereline 3.75 mg 1 month formulation

Each vial contains a triptorelin content which allows the administration of an effective dose of 3.75 mg triptorelin. After reconstitution in 2 mL of solvent, 1 mL of reconstituted suspension contains 1.875 mg of triptorelin.

Diphereline 11.25 mg 3 month formulation

Each vial contains a triptorelin content which allows the administration of an effective dose of 11.25 mg triptorelin. After reconstitution in 2 mL of solvent, 1 mL of reconstituted suspension contains 5.625 mg of triptorelin.

Diphereline 22.5 mg 6 month formulation

Each vial contains a triptorelin content which allows the administration of an effective dose of 22.5 mg triptorelin. After reconstitution in 2 mL of solvent, 1 mL of reconstituted suspension contains 11.25 mg of triptorelin.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Powder and solvent for suspension for injection, prolonged release granules.

White to off-white powder

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Diphereline is indicated for the treatment of hormone-dependent locally advanced or metastatic prostate cancer.

Diphereline 22.5 mg 6 month formulation only:

Diphereline 22.5 mg is indicated for the treatment of children 2 years and older with central precocious puberty (CPP).

4.2 DOSE AND METHOD OF ADMINISTRATION

Diphereline 3.75 mg – 1 month formulation

The recommended dose of Diphereline is 3.75 mg triptorelin (1 vial) administered once a month as a single intramuscular injection.

Diphereline 11.25 mg – 3 month formulation

The recommended dose of Diphereline is 11.25 mg triptorelin (1 vial) administered every three months as a single intramuscular injection.

Diphereline 22.5 mg – 6 month formulation

The recommended dose of Diphereline is 22.5 mg triptorelin (1 vial) administered every six months as a single intramuscular injection.

The lyophilised microgranules are to be reconstituted using 2 mL sterile water for injection (see Section 4.2 Dose and Method of Administration). The injection site should be varied periodically.

Since Diphereline is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

Special Populations

Patients with renal or hepatic impairment

No dosage adjustment is necessary for patients with renal or hepatic impairment (see also section 5.2 Pharmacokinetic properties). Diphereline must be administered under the supervision of a physician.

Paediatric population

Precocious puberty (before 8 years in girls and 9 years in boys)

Prior to initiation of treatment a clinical diagnosis of CPP should be confirmed by measurement of blood concentrations of LH (basal or stimulated with a GnRH analogue), sex steroids, and assessment of bone age versus chronological age. Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain (to rule out intracranial tumour), pelvic/testicular/adrenal ultrasound (to rule out steroid secreting tumours), human chorionic gonadotropin levels (to rule out a chorionic gonadotropin secreting tumour), and adrenal steroid measurements to exclude congenital adrenal hyperplasia.

The treatment of children with Diphereline 22.5 mg should be under the overall supervision of a paediatric endocrinologist or of a paediatrician or an endocrinologist with expertise in the treatment of central precocious puberty.

Treatment should be stopped around the physiological age of puberty in boys and girls and should not be continued in girls with a bone maturation of more than 12-13 years. There are limited data available in boys relating to the optimum time to stop treatment based on bone age, however it is advised that treatment is stopped in boys with a bone maturation age of 13-14 years.

Method of administration

The solvent for suspension should be drawn into the injection syringe and transferred to the vial containing the powder. The vial should be gently shaken to thoroughly disperse particles and obtain a uniform suspension. The suspension will appear milky. The suspension obtained should be drawn back into the injection syringe. The injection needle has to be changed and the produced suspension for injection should be administered immediately.

The suspension should be discarded if not used immediately after reconstitution.

Diphereline contains no antimicrobial agent. The product is for treatment of one patient only on one occasion. Discard any remaining contents. Used injection needles should be disposed in a designated sharp container. Any remaining product should be discarded.

Diphereline must be administered under the supervision of a healthcare professional.

4.3 CONTRAINDICATIONS

Diphereline is contraindicated in patients with known hypersensitivity to the active substance triptorelin, GnRH, other GnRH agonist analogues or to any of the excipients (see Section 6.1 List of excipients). Note that polysorbate 80 has been observed to induce hypersensitivity reactions in some patients.

Diphereline must not be administered if there are indications that the tumour is not hormone-dependent or following surgical castration.

Diphereline is contraindicated in patients with spinal cord compression secondary to prostate cancer metastases.

Diphereline is contraindicated in pregnancy and during lactation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prostate Cancer

Initially triptorelin causes a transient increase in serum testosterone levels. As a consequence, isolated cases of transient worsening of signs and symptoms of prostate cancer may occasionally develop during the first weeks of treatment. During the initial phase of treatment, consideration should be given to the additional administration of a suitable anti-androgen to counteract the initial rise in serum testosterone levels and the worsening of clinical symptoms.

A small number of patients may experience a temporary worsening of signs and symptoms of prostate cancer (tumour flare) and a temporary increase in cancer related pain (metastatic pain), which can be managed symptomatically.

As with other GnRH agonists, isolated cases of spinal cord compression or urethral obstruction have been observed. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy should be considered. Careful monitoring is indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastases, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

After surgical castration, triptorelin does not induce any further decrease in serum testosterone levels. Once the castration levels of testosterone have been achieved by the end of the first month, serum testosterone levels are maintained for as long as the patients receive their injection every one, three or six months. The effectiveness of treatment can be monitored by measuring serum levels of testosterone and prostate specific antigen.

QT prolongation

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see Section 4.5 Interactions With Other Medicines and Other Forms of Interactions) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Diphereline.

Precocious puberty

Treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.

Pseudo-precocious puberty (gonadal or adrenal tumour or hyperplasia) and gonadotropin-independent precocious puberty (testicular toxicosis, familial Leydig cell hyperplasia) should be precluded.

In girls, initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen withdrawal, may lead, in the first month, to vaginal bleeding of mild or moderate intensity.

After discontinuation of treatment the development of puberty characteristics will occur.

Information with regards to future fertility is still limited but future reproductive function and fertility appears to be unaffected by GnRH treatment. In most girls, regular menses will start on average one year after ending the therapy.

Bone mineral density may decrease during GnRH agonist therapy for central precocious puberty due to the expected effects of oestrogen suppression. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.

Slipped capital femoral epiphysis can be seen after withdrawal of GnRH agonist treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH

agonists weaken the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.

Cardiovascular disease

An 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 ratio 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 managed according to current clinical practice.

Osteoporosis and bone mineral density

The use of GnRH agonists may cause reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonate in combination with an GnRH agonist may reduce bone mineral loss. Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition).

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss and may lead to osteoporosis and increased risk of bone fracture. This may also lead to an incorrect diagnosis of bone metastases.

Depression

There is an increased risk of mood changes and incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as triptorelin. Patients should be informed accordingly and treated as appropriate if symptoms occur. Patients with known depression should be monitored closely during therapy.

Hyperglycaemia and Diabetes

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Patients may experience metabolic changes (e.g. glucose intolerance, fatty liver). Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or glycosylated haemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for the treatment of hyperglycaemia or diabetes.

Other identified precautions

Treatment with GnRH analogues may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. These patients may present a pituitary apoplexy which is characterised by sudden headache, vomiting, visual impairment and ophthalmoplegia.

Adjustment of antihypertensive therapy may be required in patients receiving such medication.

Caution is required with intramuscular injection in patients treated with anticoagulants, due to the potential risk of haematomas at the site of injection.

Administration of triptorelin in therapeutic doses results in suppression of the pituitary gonadal system. Normal function is usually restored after treatment is discontinued. Diagnostic tests of pituitary gonadal function conducted during treatment and after discontinuation of therapy with a GnRH agonist may therefore be misleading.

Pseudotumour cerebri (PTC) / idiopathic intracranial hypertension has been reported in women and children receiving GnRH analogues including triptorelin. Monitor patients for signs and symptoms of PTC/ idiopathic intracranial hypertension, including severe or recurrent headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea. Refer the patient to an ophthalmologist to confirm the presence of papilledema. If PTC/idiopathic intracranial hypertension is confirmed, treat the patient in accordance with established treatment guidelines and permanently discontinue use of triptorelin.

Convulsions have been reported with GnRH analogues, particularly in women and children. Some of these patients had risk factors for seizures (such as a history of epilepsy, intracranial tumours or co-medication with drugs known to present a risk of seizure reactions). Convulsions have also been reported in patients in the absence of such risk factors.

Due to androgen deprivation, treatment with analogues of GnRH can increase the risk of anaemia in men. This risk should be assessed in treated patients and monitored appropriately.

All formulations of Diphereline contain less than 1 mmol (23 mg) sodium per dose.

Use in the elderly

No data available.

Paediatric use

The Diphereline 22.5 mg 6 month formulation is indicated for use in children 2 years and older with central precocious puberty (CPP).

The safety and efficacy of triptorelin embonate 3.75 mg (1 month) and 11.25 mg (3 month) formulations have not been reviewed in neonates, infants, children and adolescents, and are therefore not indicated for use in these populations.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Diphereline 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, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see Section 4.4 Special Warnings and Precautions for Use).

When triptorelin is co-administered with drugs affecting pituitary secretion of gonadotrophins, caution should be given and it is recommended that the patient's hormonal status should be supervised.

In the absence of relevant data, there is a theoretical risk that treatment with drugs that increase serum prolactin may decrease the efficacy of GnRH agonists as hyperprolactinaemia reduces the number of pituitary GnRH receptors.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In chronic toxicity studies at clinically relevant doses, triptorelin induced changes in the reproductive organs of male rats, dogs and monkeys. These were considered to reflect the suppressed gonadal function caused by the pharmacological activity of the compound. These changes would be expected to cause a profound impairment of fertility but, were partly reversed (males) or largely reversed (females) after cessation of treatment. In males, changes included decreases in weight and atrophic histological changes in the testes, epididymis, seminal vesicle and prostate gland, with suppression of spermatogenesis. In females, changes included ovarian atrophy and suppression of ovarian function, with arrest of follicular development and cessation of oestrus cycling; uterine weights were also reduced.

Use in pregnancy (Category D)

Safe use of Diphereline 22.5 mg in pregnancy has not been established in clinical studies. It should be confirmed that the patient is not pregnant before prescription of Diphereline 22.5 mg.

Diphereline should not be used during pregnancy since concurrent use of GnRH agonists is associated with a theoretical risk of abortion or foetal abnormality.

After subcutaneous administration of 10 micrograms/kg/day to rats on days 6 to 15 of gestation, triptorelin did not elicits any embryotoxicity or teratogenicity. At 100 micrograms/kg/day, a reduction in maternal body weight gain and an increased number of resorptions were observed.

Use in lactation

Diphereline is not recommended for use during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However the ability to drive and use machines may be impaired should the patient experience dizziness, somnolence, epileptic seizures and visual disturbances being possible undesirable effects of treatment, or resulting from the underlying disease.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

General tolerance in men

Since patients suffering from locally advanced or metastatic, hormone-dependent prostate cancer are generally old and have other diseases frequently encountered in this aged population, most of the patients included in clinical trials reported adverse events. As seen with other GnRH agonist therapies or after surgical castration, the most commonly observed adverse events related to triptorelin treatment were due to its expected pharmacological effects: Initial increase in testosterone levels, followed by almost complete suppression of testosterone. These effects included hot flushes (50%), erectile dysfunction (4%) and decreased libido (3%).

With the exception of immuno-allergic reactions (0.2%) and injection site reactions (3%), all adverse reactions are known to be related to testosterone changes.

Tabulated list of adverse reactions in men

The following adverse reactions, considered as at least possibly related to triptorelin treatment, were reported. Most of these are known to be related to biochemical or surgical castration.

In Table **1**, the frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000). No very rare (<1/10000) adverse reactions were reported.

Table 1: Adverse reactions in men

System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**	**Additional post-marketing adverse events**
	≥ 10%	**≥1% - <10%**	**≥0.1% - <1%**	**≥0.01% - <0.1%**	**Unknown freqeuncy**
Blood and lymphatic system disorders			Thrombocytosis		Anaemia
Cardiac disorders			Palpitations		QT prolongation[4]
Ear and labyrinth disorders			Tinnitus Vertigo		
Endocrine disorders					Pituitary apoplexy[2]
Eye disorders			Visual impairment	Abnormal sensation in eye Visual disturbance	
Gastrointestinal disorders		Nausea Dry mouth	Abdominal pain Constipation	Abdominal distension	

System Organ Class	Very Common	Common	Uncommon	Rare	Additional post-marketing adverse events
	≥ 10%	≥1% - <10%	≥0.1% - <1%	≥0.01% - <0.1%	Unknown freqeuncy
			Diarrhoea Vomiting	Dysgeusia Flatulence	
General disorders and administration site conditions	Asthenia	Injection site erythema, inflammation, pain, reaction Oedema	Lethargy Oedema peripheral Pain Rigors Somnolence	Chest pain Dysstasia Influenza like illness Pyrexia	Malaise
Immune system disorders		Hypersensitivity		Anaphylactic reaction	Anaphylactic shock
Infections and infestations				Nasopharyngitis	
Investigations		Weight increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased Blood pressure increased Blood urea increased Gamma-glutamyl transferase increased Weight decreased	Blood alkaline phosphatase increased	
Metabolism and nutrition disorders			Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite		
Musculoskeletal and connective tissue disorders	Back pain	Musculo-skeletal pain Pain in extremity	Arthralgia Bone pain Muscle cramp Muscular weakness Myalgia	Joint stiffness Joint swelling Musculoskeletal stiffness Osteoarthritis	
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	Convulsions[3]
Psychiatric disorders	Libido decreased	Loss of libido Depression* Mood changes*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety

System Organ Class	Very Common	Common	Uncommon	Rare	Additional post-marketing adverse events
	≥ 10%	≥1% - <10%	≥0.1% - <1%	≥0.01% - <0.1%	Unknown freqeuncy
Renal and urinary disorders			Nocturia Urinary retention		Urinary incontinence
Reproductive system and breast disorders	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic pain	Gynaecomastia Breast pain Testicular atrophy Testicular pain		
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	Orthopnoea	
Skin and subcutaneous tissue disorders	Hyperhydrosis		Acne Alopecia Erythema Pruritus Rash Urticaria	Blister Purpura	Angioneurotic oedema
Vascular disorders	Hot flush	Hypertension		Hypotension	

[1] This frequency is based on class-effect frequencies common for all GnRH agonists.
[2] Reported following initial administration in patients with pituitary adenoma
[3] During post market experience convulsions have been reported in patients receiving GnRH analogues, including triptorelin.
[4] see Section 4.4 Special Warnings and Precautions for Use and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions

Triptorelin causes a transient increase in circulating testosterone levels within the first week after the initial injection of the sustained release formulation. With this initial increase in circulating testosterone levels, a small percentage of patients (≤ 5%) may experience a temporary worsening of signs and symptoms of their prostate cancer (tumour flare), usually manifested by an increase in urinary symptoms (< 2%) and metastatic pain (5%), which can be managed symptomatically. Isolated cases of exacerbation of disease symptoms, either urethral obstruction or spinal cord compression by metastasis have occurred. Therefore, patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction should be closely observed during the first few weeks of therapy (see Section 4.4 Special Warnings and Precaution for Use).

The use of synthetic GnRH agonists, to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture. This may also lead to an incorrect diagnosis of bone metastases.

General tolerance in children

Tabulated list of adverse reactions in children

The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000, <1/100).

Table 2: Adverse reactions in children

System Organ Class	Very Common Treatment related AEs	Common Treatment related AEs	Uncommon Treatment related AEs	Additional Post-marketing Frequency unknown
Eye disorders			Visual impairment	Visual disturbance
Gastrointestinal disorders		Abdominal pain	Vomiting Constipation Nausea	
General disorders and administration site conditions		Injection site reaction (including injection site pain, injection site erythema and injection site inflammation)	Malaise	
Immune system disorders		Hypersensitivity		Anaphylactic shock
Investigations		Weight increased		Blood pressure increased Blood prolactin increased
Metabolism and nutrition disorders			Obesity	
Musculoskeletal and connective tissue disorders			Neck pain	Myalgia
Nervous system disorders		Headache		Pseudotumour cerebri / idiopathic intracranial hypertension Convulsions*
Psychiatric disorders			Mood altered	Affect lability Depression Nervousness
Reproductive system and breast disorders	Vaginal bleeding (including vaginal haemorrhage, withdrawal bleed, uterine haemorrhage, vaginal discharge, vaginal bleeding including spotting)		Breast pain	
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Skin and subcutaneous tissue disorders		Acne	Pruritus Rash Urticaria	Angioneurotic oedema

System Organ Class	Very Common Treatment related AEs	Common Treatment related AEs	Uncommon Treatment related AEs	Additional Post-marketing Frequency unknown
Vascular disorders		Hot flush		Hypertension

* During post market experience convulsions have been reported in patients receiving GnRH analogues, including triptorelin

General

Increased lymphocyte count has been reported with patients undergoing GnRH analogue treatment. This secondary lymphocytosis is apparently related to GnRH induced castration and seems to indicate that gonadal hormones are involved in thymic involution.

Uncommonly pressure sensitive infiltrations at the injection site have been reported in other triptorelin products after subcutaneous injection.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

The pharmaceutical properties of Diphereline and its route of administration make accidental or intentional overdose unlikely. There is no experience of overdose from clinical trials. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentration and on the reproductive tract will be evident with higher doses of Diphereline.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Hormones and related agents, gonadotropin releasing hormone analogues

ATC code: L02AE04

Mechanism of action

Triptorelin, a gonadotrophin releasing hormone (GnRH) agonist, inhibits gonadotrophin secretion when given continuously and in therapeutic doses. Male animal and human studies show that after the administration of triptorelin there is an initial and transient increase in circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. However, chronic and continuous administration of triptorelin results in decreased LH and FSH secretion and suppression of testicular and ovarian steroidogenesis. A reduction of serum testosterone levels into the range normally seen in surgically castrated men occurs approximately 2 to 4 weeks after initiation of therapy. This results in accessory sexual organ atrophy. These effects are generally reversible upon discontinuation of the medicinal product.

In animals, administration of triptorelin resulted in the inhibition of growth of some hormone-sensitive prostate tumours in experimental models.

Clinical trials

Prostate Cancer

One pivotal, long-term (9 months), controlled, Phase III, multicentre study (DEB-96-TRI-01, first phase) compared the 3.75 mg (1 month) and 11.25 mg (3 month) embonate formulations in 348 patients with advanced prostatic cancer. Patients in this study had histologically confirmed stage C (52.9% of patients) or D (46.8% of patients) prostate cancer with testosterone levels greater than 5 nmol/L at baseline. The mean age of the 348 patients in the safety population was 70.5 years (range 45 to 96 years); mean age at onset of prostate cancer was 69.8 years (range 44 to 96 years) and the mean disease duration was 6.9 months (range 0 to 155 months).

Per protocol and intent-to-treat analyses produced similar results. The 3-month formulation was non-inferior (no worse than 10 percentage point difference in incidence) to the 1-month formulation in inducing and maintaining chemical castration (Table **3**).

Table 3: Chemical Castration in Advanced Prostate CancerTrial DEB-96-TRI-01 Phase 1 per protocol population

Parameter	Triptorelin 11.25 mg q 12w (n=166)	Triptorelin 3.75 mg q 4w (n=159)	Difference [95% CI][4]
Induction by day 29[1,2]	97.6%	92.5%	5.1% [-1.1%, 13.8%]
Maintenance 2-9 mths[3]	94.1%	95.3%	-1.2% [-6.3%, 3.9%]
LH increase ≤ 1.0 IU/L – Day 85	92.5%	97.4%	-4.9% [-13.6%, 1.4%]
LH increase ≤ 1.0 IU/L – Day 169	92.4%	98.6%	-6.2% [-15.3%, -0.1%]*

[1] Serum testosterone < 1.735 nmol/L.
[2] Chemical castration was achieved by day 57 in most patients.
[3] Kaplan-Meier estimate.
[4] A lower bound > -10% demonstrates non-inferiority between treatments.
* 1-month formulation significantly better.

The second phase of study DEB-96-TRI-01 (9 months) compared the efficacy of the 1 month formulation of triptorelin 3.75 mg and the US 1 month formulation of leuprorelin acetate 7.5 mg in patients with advanced prostatic cancer (the US formulation of leuprorelin acetate is not the same as the Australian-registered formulation). This study involved 284 patients who had histologically confirmed stage C or D prostatic cancer.

Per protocol and intent-to-treat analyses produced similar results. Whilst the 1-month formulation was slower in inducing chemical castration than the US 1-month leuprorelin acetate formulation, it was non-inferior in maintaining chemical castration (no worse than 10 percentage point difference in incidence) – Table **4**.

Table 4: Chemical Castration in Advanced Prostate Cancer Trial DEB-96-TRI-01 Phase 2 per protocol population.

Parameter	Triptorelin 3.75 mg q 4w (n=135)	Leuprorelin[5] 7.5 mg q 4w (n=137)	Difference [95% CI][4]
Induction by day 29[1,2]	91.1%	99.3%	-8.2% [-17.1%, 1.4%]*
Maintenance 2-9 mths[3]	96.1%	93.1%	3.0% [-2.5%, 8.6%]
LH increase ≤ 1.0 IU/L – Day 85	98.4%	93.6%	4.8% [-1.9%, 15.0%]
LH increase ≤ 1.0 IU/L – Day 169	98.3%	93.8%	4.5% [-3.0 %, 15.0%]

[1] Serum testosterone < 1.735 nmol/L.
[2] Chemical castration was achieved by day 57 in most patients.
[3] Kaplan-Meier estimate.
[4] A lower bound > -10% demonstrates non-inferiority between treatments.
[5] US formulation not available in Australia.
* Leuprorelin significantly better.

With continuous use, desensitisation of the pituitary gonadotrophin receptors had generally occurred by 84 days of exposure making a surge in serum testosterone unlikely after this time – Table **3** & Table **4** show that most patients had minimal increases in serum LH (≤ 1.0 IU/L) at days 85 and 169.

In trial DEB-TRI6M-301, 120 patients with advanced prostate cancer received Diphereline 22.5 mg 6-month formulation IM on days 1 and 169 and were followed until Day 337 (48 weeks). The median age of patients was 70 years (range 50 – 92). The primary efficacy endpoints were the percentage of patients achieving the castrate level of testosterone (≤ 1.735 nmol/L) by Day 29 and percentage of patients maintaining this level from day 57 to Week 48. 115 patients (96%) completed the study. Three patients died, one was lost to follow-up and one withdrew consent. Of the patients completing the trial, 93% maintained castrate serum testosterone levels from Day 57 to Week 48 (Table 4 per protocol population). Intent-to-treat results were similar.

Table 5: Chemical Castration in Advanced Prostate Cancer Trial DEB-TRI6M-301 per protocol population

Parameter	Triptorelin 22.5 mg q 24w n = 115	95% CI
Induction by Day 29[1]	97.4 %	[92.6%, 99.5%]
Maintenance 2-9 months[2]	93.9 %	[89.5%, 98.3%]
Maintenance 2-12 months (48 weeks) [2]	93.0 %	[88.3%, 97.7%]
LH increase ≤ 1.0 IU/L – Day 169	98.2 % (n=114)	[93.8%, 99.8%]

[1] Serum testosterone ≤ 1.735 nmol/L.
2.Kaplan-Meier estimate.

Precocious puberty
Inhibition of the increased hypophyseal gonadotropic activity in children with precocious puberty leads to lowering of the LH levels following GnRH (or GnRH agonist) stimulation test and to suppression of oestradiol and testosterone secretion in girls and boys, respectively.

In a non-comparative clinical study, 44 children with central precocious puberty (39 girls and 5 boys) were treated with a total of two intramuscular injections of Diphereline 22.5 mg over 12 months (48 weeks). Suppression of stimulated LH concentrations to prepubertal levels (serum LH $\leq$ 5 IU/L) was achieved in 95.5% of subjects by month 3, and in 93.2 % and 97.7% of subjects at months 6 and 12, respectively.

The consequence is a regression or stabilisation of secondary sex characteristics and slowing down of accelerated bone maturation and growth.

In girls, initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen increase, may lead, in the first month, to uterine 'withdrawal' bleeding of mild or moderate intensity.

The mean chronological age was 94.6 months (range: 31.0 to 118.0 months). The Tanner stage was stable or reduced in 90.9% of patients between baseline and Month 6 and in 88.6% patients between baseline and Month 12.

Table 6: Tanner Puberty Stage in Precocious Puberty Study

Tanner Puberty Stage	**ITT** **n=44**	**PP** **n=43**
Month 6 (Day 169)		
No increase from baseline 95%CI	40 / 44 (90.91%) (78.33% ; 97.47%)	39 / 43 (90.70%) (77.86% ; 97.41%)
Month 12 (Day 337)		
No increase from baseline 95%CI	39 / 44 (88.64%) (75.44%; 96.21%)	38 / 43 (88.37%) (74.92%; 96.11%)

The percentage of children with no increase, i.e. reduction or stabilisation, of bone age/chronological age ratio on-treatment was 63.6% at Month 6 and 95.5% at Month 12.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In a sub-study of the pivotal efficacy trial DEB-96-TRI-01 of the 1- and 3-month doses in patients with prostate cancer, triptorelin exposure based on plasma AUC was comparable after intramuscular doses of the 1-month (x 3 doses at 28-day intervals) and 3-month formulations of triptorelin embonate (**Table 7**). Triptorelin did not accumulate over 9 months of treatment.

In a sub-study in 15 patients with prostate cancer from the efficacy trial of the 6 month formulation (DEB-TRI6M-301), the plasma C_{max} after the first injection was comparable to that obtained previously with the 3-month formulation and higher than the 1-month formulation; however, the AUC over 6 months (resulting from an overall dose of 22.5 mg for all 3 formulations) was about half that after the 3-month and 1-month formulations.

The three sustained release formulations of Diphereline cannot be considered strictly bioequivalent and this is due to differences in polymeric matrix which confers different release rate for each of the three strengths. Nonetheless, the three formulations were demonstrated to be pharmacodynamically equivalent.

The relationship between serum triptorelin and serum testosterone is not linear but on/off, so the level of serum triptorelin rather than AUC is important in maintaining castrate serum testosterone levels. After an initial surge, mean ± SD serum testosterone remained below the castrate level (≤ 1.735 nmol/L) for the 336 days of the trial, except at Day 336 when the upper limit of the standard deviation was above the castrate level.

Table 7: Pharmacokinetic Parameters of 1-Month, 3-Month And 6-Month Formulations of triptorelin embonate

Formulation	N	Geometric Mean (range) C_{max} *after 1st injection (ng/mL)*	Median (Range) T_{max} after 1st injection *(hours)*	Geometric Mean AUC over 6 months* *(days.ng/mL)*
1-month (3.75 mg x 3 doses)	14	15.6 (9.1-25.2)	2 (2-4)	197.9 (101.8-452.6) ($AUC_{(169-253d)}$ x 2)
3-month (11.25 mg)	13	35.8 (16.5-57.4)	2 (1-4)	202.3 (117.6-325.2) ($AUC_{(169-253d)}$ x 2)
6-month (22.5mg)	15	40.0 (22.2-76.8)	3 (2-12)	111.5 (52.2-177.4) $AUC_{169-337d}$

*Cumulative AUC over 6 month period (corresponding to 22.5 mg overall: 6 injections of 1-month, 2 injections of 3-month and 1 injection of the 6-month formulation)

In a study in healthy volunteers, the absolute bioavailability of an intramuscular dose of the 1-month formulation was 83%.

In children with precocious puberty median t_{max} was 4 (2-8) hours and C_{max} following the first injection was 39.9 (19.1-107.0) ng/ml.

Distribution

Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous bolus administration, triptorelin is distributed and eliminated according to a

3-compartment model and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.

The volume of distribution at steady state of triptorelin following intravenous administration of 0.5 mg triptorelin is approximately 30 L in healthy male volunteers. Since there is no evidence that triptorelin at clinically relevant concentrations binds to plasma proteins, medicinal product interactions involving binding-site displacement are unlikely.

Metabolism

Metabolites of triptorelin have not been determined in humans. However, human pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded within tissues or are rapidly further degraded in plasma, or cleared by the kidneys.

Excretion

Triptorelin is eliminated by both the liver and the kidneys. Following intravenous administration of intermediate-release triptorelin acetate 0.5 mg to 6 young healthy adult males (mean Cl_{creat} 150 mL/min), 42% of the dose was excreted in the urine as intact triptorelin. The mean triptorelin clearance was 212 mL/min.

Pharmacokinetics in special patient populations

Renal and hepatic impairment

In the intravenous study referred to under Excretion, patients with renal and liver impairment were also studied. There were 6 subjects in each group. Compared to young healthy adult males, mean triptorelin clearance was reduced by 43% in subjects with moderate renal impairment (mean Cl_{creat} 40 mL/min), 58% in subjects with severe renal impairment (mean Cl_{creat} 8.9 mL/min) and 73% in subjects with hepatic impairment (Child Pugh score 5-9) and a lower mean Cl_{creat} (90 mL/min) than young healthy adult males. Triptorelin exposure was increased 2- to 4-fold in patients with renal or hepatic impairment.

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied. However, pharmacokinetic data obtained in young healthy male volunteers aged 20 to 22 years with an elevated creatinine clearance (approximately 150 mL/min) indicated that triptorelin was eliminated twice as fast in the young population. This is related to the fact that triptorelin clearance is correlated to total creatinine clearance, which is well known to decrease with age.

Because of the large safety margin of triptorelin and since Diphereline is a sustained release formulation, no dose adjustment is recommended in patients with renal or hepatic impairment.

Pharmacokinetic/pharmacodynamic relationship(s)

The pharmacokinetics/pharmacodynamics relationship of triptorelin is non-linear and time-dependent. Thus, after acute administration in naive subjects, triptorelin induces a dose-dependent increase of LH and FSH responses.

When administered as a sustained release formulation, triptorelin stimulates LH and FSH secretion during the first days post dosing and, in consequence, testosterone secretion. As shown by the results of the different bioequivalence studies, the maximal increase in testosterone is reached after around 4 days with an equivalent c_{max} which is independent from the release rate of triptorelin. This initial response is not maintained despite continuous exposure to triptorelin and is followed by a progressive decrease of testosterone levels. In this case too, the extent of triptorelin exposure can vary markedly without affecting the overall effect on testosterone serum levels.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In vitro genotoxicity tests for gene mutations and chromosomal damage, and a mouse micronucleus test have provided no evidence for genotoxic effects.

Carcinogenicity

Carcinogenicity studies were conducted in mice (18 months) and rats (23 months) with triptorelin embonate microgranules administered once monthly IM. In mice, no oncogenic effect was observed at triptorelin doses of up to 6000 micrograms/kg/month. In rats, an almost 100% incidence of pituitary tumours was observed at each dose level (120, 600 and 3000 micrograms/kg/month), leading to premature death. There were increased incidences of both pituitary adenomas and carcinomas at all dose levels. The increased incidence of pituitary tumours in rats is a common effect associated with GnRH agonist treatment. The clinical relevance of this is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Composition of the Powder: polyglactin, mannitol, carmellose sodium, polysorbate 80.

Composition of the Solvent: Water for Injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After opening

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the prepared suspension should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

Contains no antimicrobial preservative. Use each ampoule in one patient on one occasion only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

For storage conditions after first opening of the medicinal product, see Section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

Diphereline 3.75 mg 1 month formulation

6 mL type I brown tint glass vial with grey bromobutyl stopper and purple aluminium flip-off capsule.

Diphereline 11.25 mg 3 month formulation

6 mL type I brown tint glass vial with grey bromobutyl stopper and yellow green aluminium flip-off capsule.

Diphereline 22.5 mg 6 month formulation

6 mL type I brown tint glass vial with grey bromobutyl stopper and dark green aluminium flip-off capsule.

Solvent: Type I glass ampoule containing 2 mL of sterile solvent for suspension.

Each box contains 1 vial, 1 ampoule and 1 blister containing 1 empty polypropylene injection syringe and 2 injection needles.

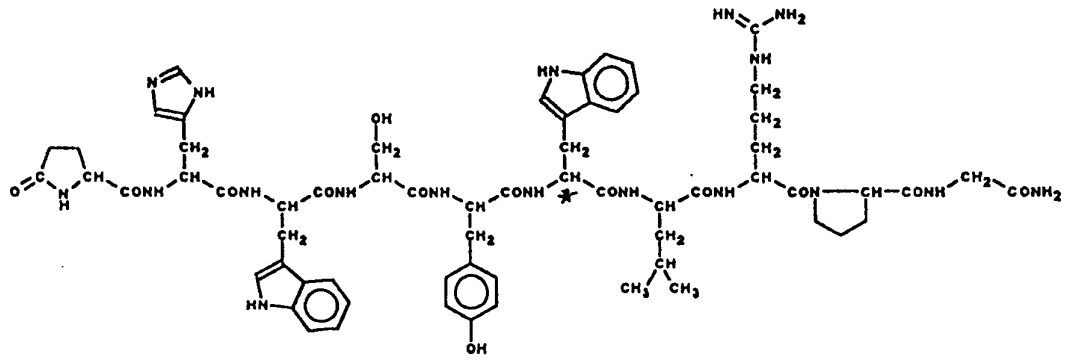
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

[(L-Pyr)-(L-His)-(L-Trp)-(L-Ser)-(L-Tyr)-(D-Trp)-(L-Leu)-(L-Arg)-(L-Pro)-(Gly-NH_2)]



Molecular formula: $C_{64}H_{82}N_{18}O_{13}$ (triptorelin). $C_{23}H_{16}O_6$ (embonate)

Molecular weight: 1311.5 (triptorelin) + 388.4 (embonate)

CAS number

57773-63-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Ipsen Pty Ltd
Level 5
627 Chapel Street
South Yarra Victoria 3141

Telephone: 1800 317 033

9 DATE OF FIRST APPROVAL

28 August 2006

10 DATE OF REVISION

11 December 2024

Summary table of changes

Section changed	Summary of new information
4.3	Addition of Contraindication regarding not administering the product if the tumour is not hormone-dependent or following surgical castration