AUSTRALIAN PRODUCT INFORMATION - DECAPEPTYL® (TRIPTORELIN ACETATE) 100 MICROGRAMS/1 ML SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Triptorelin acetate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DECAPEPTYL is for subcutaneous (s.c.) injection.

It consists of a clear, colourless solution containing 100 micrograms of triptorelin acetate (equivalent to 95.6 micrograms of triptorelin free base) in a pre-filled syringe. The concentration of triptorelin is 95.6 micrograms/1 mL (equivalent to triptorelin acetate 100 micrograms/1 mL).

DECAPEPTYL contains sodium chloride, glacial acetic acid and water for injections.

3 PHARMACEUTICAL FORM

Triptorelin is a white to off-white powder, freely soluble in acetic acid, and soluble in water and in diluted acids and bases.

Appearance of the injection: Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DECAPEPTYL 100 micrograms/1 mL is indicated for down-regulation and prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian stimulation for assisted reproductive technologies (ART).

In clinical trials, DECAPEPTYL 100 micrograms/1 mL has been used in cycles where urinary and recombinant human follicle stimulating hormone (FSH) as well as human menopausal gonadotrophin (HMG) were used for stimulation.

4.2 DOSE AND METHOD OF ADMINISTRATION

The dosage regimen of DECAPEPTYL is 100 micrograms given once daily as a 1 mL subcutaneous injection into the lower abdominal wall. Treatment with DECAPEPTYL 100 micrograms/1 mL should be initiated under the supervision of a physician experienced in the treatment of infertility. Following the first administration, it is advised that the patient be kept under medical supervision for 30 minutes to ensure there is no allergic/pseudo-allergic reaction to the injection.

Subsequent injections of DECAPEPTYL may be self-administered by the patient. In this instance the patient should first be instructed on appropriate self-injection technique and be made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention should such a reaction occur. For detailed information on how to inject DECAPEPTYL, the patient should refer to the “Patient Instructions for Use Leaflet” provided with the product.

Injecting the medicine

1. Remove the protective foil and take the syringe out of the blister packaging
2. Keep the syringe upright with the grey protective cap facing up

3. Remove the grey protective cap
4. Gently push the plunger until the first drops of liquid appear at the needle tip
5. The medicine is to be injected under the skin of the lower abdomen. Clean the injection site with an antiseptic swab immediately prior to injection
6. Lift up a fold of skin between thumb and forefinger. With your free hand hold the syringe at a right angle to the skin like a dart and quickly insert the needle all the way into the skin fold. Press down slowly on the plunger to inject the contents of the syringe
7. Remove the syringe and needle from the skin and discard this immediately into a sharps disposal unit
8. For each dose, choose a different injection site along the lower abdomen.

Treatment can be started in the early follicular phase (day 2 or 3 of the menstrual cycle) or in the mid-luteal phase (day 21-23 of the menstrual cycle or 5-7 days before expected start of menses). Controlled ovarian stimulation with gonadotropins should be started after approximately 2-4 weeks of DECAPEPTYL treatment. Ovarian response should be monitored clinically (including ovarian ultrasound alone or preferably in combination with measurement of oestradiol levels) and the dose of gonadotropins adjusted accordingly.

When a suitable number of follicles have reached an appropriate size, treatment with DECAPEPTYL and gonadotropin is stopped and a single injection of human chorionic gonadotrophin (hCG) is administered to induce the final follicular maturation. If down-regulation is not confirmed after 4 weeks (determined by ultrasound documentation of a shedded endometrium alone or preferably in combination with measurement of oestradiol levels), discontinuation of DECAPEPTYL should be considered. The total duration of treatment is usually 4-7 weeks.

When using DECAPEPTYL, luteal phase support should be provided according to the reproductive medical centre's practice.

No specific dose recommendations are given for subjects with renal or hepatic impairment. A clinical study indicated that the risk of accumulation of triptorelin in patients with severe liver and renal impairment is small (see **Section 5.2 – PHARMACOKINETIC PROPERTIES**).

4.3 CONTRAINDICATIONS

DECAPEPTYL 100 micrograms/1 mL is contraindicated in cases of:

- Hypersensitivity to triptorelin or to any of the excipients in DECAPEPTYL
- Hypersensitivity to gonadotropin-releasing hormone (GnRH) or any other GnRH analogue
- Pregnancy and lactation
- Women of childbearing potential should be examined carefully before treatment to exclude pregnancy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

ART is associated with an increased risk of multiple pregnancies, pregnancy loss, ectopic pregnancies and congenital malformations. These risks are also valid with usage of DECAPEPTYL as adjunct therapy in controlled ovarian stimulation.

Follicular recruitment, induced by gonadotrophins following treatment with GnRH analogues, may be markedly increased in a minority of predisposed patients, particularly in case of Polycystic Ovarian Syndrome (PCOS).

Ovarian stimulation should be conducted under strict medical supervision.

Ovarian Hyperstimulation Syndrome

The use of DECAPEPTYL in controlled ovarian stimulation may increase the risk of ovarian hyperstimulation syndrome (OHSS) and ovarian cysts. As with other GnRH analogues there have been reports of OHSS associated with the use of triptorelin in combination with gonadotropins.

OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

The following symptoms may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events.

Excessive ovarian response to gonadotropin treatment seldom gives rise to OHSS unless hCG is administered to trigger ovulation. Therefore in cases of OHSS it is prudent to withhold hCG and advise the patient to refrain from coitus or to use barrier methods for at least 4 days. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after the hCG administration.

OHSS may be more severe and more protracted if pregnancy occurs. This syndrome occurs with higher incidence in patients with polycystic ovarian disease. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum severity at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If severe OHSS occurs, gonadotropin treatment should be stopped if still ongoing, the patient hospitalised and specific therapy for OHSS started e.g. with rest, intravenous infusion of electrolyte solutions or colloids and heparin.

The risk of OHSS might be higher with use of GnRH agonists in combination with gonadotropins than with use of gonadotropins alone. In two clinical studies (MFK/IVF/0399E and FE999906 CS003), GnRH agonists, including DECAPEPTYL, were used in combination with gonadotropins, OHSS was reported in 6.5% and 3.1% of patients respectively.

Ovarian cysts

Ovarian cysts may occur during the initial phase of treatment with GnRH agonists. They are usually asymptomatic and non-functional.

Bone loss

Long term use of GnRH agonists may cause reduction in bone mineral density. Patients with known risk of osteopenia should discuss this with the treating physician. In view of the possible effect on bone density, GnRH agonist therapy without add-back therapy should not exceed duration of 6 months.

Drugs/conditions affecting pituitary secretion

Rarely, treatment with GnRH agonists may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. These patients may present with a pituitary apoplexy characterised by sudden headache, vomiting, visual impairment and ophthalmoplegia. When triptorelin is co-administered with drugs affecting pituitary secretion of gonadotropins caution should be exercised and it is recommended that the patient's hormonal status should be supervised.

Depression and mood changes

There is an increased risk of depression in patients undergoing treatment with GnRH agonists, such as triptorelin. Patients should be informed accordingly and treated as appropriate if symptoms occur. Mood changes, including depression have been reported during long term use.

Patients with known depression should be monitored closely during therapy**.**

Use in atopic patients

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with DECAPEPTYL is not advised in women with severe allergic conditions.

Use in Hepatic Impairment

In patients with hepatic impairment, triptorelin has a mean terminal half-life of 7-8 hours compared to 3-5 hours in healthy subjects (see **Section 5.2 PHARMACOKINETIC PROPERTIES**). Despite this prolonged exposure, triptorelin is not expected to be present in circulation at the time of embryo transfer.

Use in Renal Impairment

In patients with renal impairment, triptorelin has a mean terminal half-life of 7-8 hours compared to 3-5 hours in healthy subjects (see **Section 5.2 PHARMACOKINETIC PROPERTIES**). Despite this prolonged exposure, triptorelin is not expected to be present in circulation at the time of embryo transfer.

Use in the Elderly

DECAPEPTYL, a product for use in ART, is not indicated for use in the elderly.

Paediatric use

DECAPEPTYL, a product for use in ART, is not indicated for use in the paediatric population.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions of DECAPEPTYL 100 micrograms/1 mL with other medicines have not been investigated for this indication.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

DECAPEPTYL is indicated for use in assisted reproductive technologies (see **Section 4.1 - THERAPEUTIC INDICATIONS**).

Use in Pregnancy (Category D)

DECAPEPTYL 100 micrograms/1 mL is contraindicated during pregnancy (see **Section 4.3 CONTRAINDICATIONS**). Pregnancy must be excluded before initiation of fertilisation treatment. Non-hormonal methods of contraception should be employed during therapy until menses resume. If a patient becomes pregnant while receiving triptorelin, therapy should be discontinued.

When triptorelin is used for fertilisation treatment, there is no non-clinical or clinical evidence to suggest a causal connection between triptorelin and any subsequent abnormalities of oocyte development or pregnancy or outcome.

Very limited clinical data on the use of triptorelin during pregnancy does not indicate an increased risk of congenital malformations. Treatment of pregnant rats with triptorelin acetate at 10 micrograms/kg/day by subcutaneous administration during early pregnancy resulted in delayed fetal development and treatment in mid-pregnancy resulted in inhibition of parturition with frequent stillbirths. Administration of the drug during the period of organogenesis revealed no evidence of teratogenicity in rats or rabbits at subcutaneous doses up to 10 and 50 micrograms/kg/day, respectively (0.9 and 9 times the clinical dose on a body surface area basis). Based on the pharmacological effects, disadvantageous influence on the pregnancy and the offspring cannot be excluded.

Use in Lactation
DECAPEPTYL is contraindicated for use during lactation (see **Section 4.3 CONTRAINDICATIONS**).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of the ability to drive and use machines have been performed. However, due to its pharmacological profile DECAPEPTYL 100 micrograms/1 mL is likely to have no or negligible influence on the patient's ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The information presented in **Table 1** is based on adverse events (AEs) and adverse drug reactions (ADRs), and their frequencies, reported in clinical trials of DECAPEPTYL 100 micrograms daily in down-regulation and prevention of premature LH surges (N=2095).

The following criteria were used in the selection of AEs/ADRs that are presented throughout this section.

1. Clinical trials: Treatment-Emergent AEs reported by at least 1% of the ART subjects receiving DECAPEPTYL 100 micrograms daily
2. Post-marketing safety surveillance: > 3 ADR reports of the ART subjects receiving DECAPEPTYL 100 micrograms daily.

The most frequent adverse events are headache, injection site erythema, ovarian cyst, abortion, dysmenorrhoea, ovarian hyperstimulation syndrome, injection site inflammation and nausea. Ovarian cysts have been reported to occur during the initial phase of treatment with DECAPEPTYL. When used for infertility treatment, ovarian hyperstimulation syndrome (see **Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE**), ovarian enlargement, dyspnoea, pelvic and/or abdominal pain may be observed.

No anaphylactic reactions have been seen in clinical trials.

Table 1: Listing of AEs/ADRs reported in clinical trials, according to frequency, in patients who received DECAPEPTYL 100 micrograms daily.

MedDRA System organ class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to ≤ 1/100)	Rare (≥1/10,000 to <1/1,000)
Infections and infestations		Upper respiratory tract infection, Pharyngitis	
Immune system disorders		Hypersensitivity***	
Psychiatric disorders		Mood altered*, Depression*	Fear
Nervous system disorders	Headache	Dizziness	
Vascular disorders		Hot flushes	
Respiratory, thoracic and mediastinal disorders			Dyspnoea
Gastrointestinal disorders	Nausea	Abdominal pain, Vomiting	
Skin and subcutaneous tissue disorders		Hyperhidrosis, Rash	Pruritus, Blister
Musculoskeletal and connective tissue disorders		Musculoskeletal pain, Back pain	
Pregnancy, puerperium and perinatal conditions	Abortion		
Reproductive system and breast disorders	Ovarian cyst**, Ovarian hyperstimulation syndrome, Dysmenorrhoea	Breast pain, Pelvic pain	Vaginal discharge
General disorders and administration site conditions	Injection site inflammation, Injection site erythema	Injection site pain, Fatigue	Injection site discolouration, Injection site irritation, Cyst

*This frequency is based on class-effect frequencies common for all GnRH agonists.
** Ovarian cysts may occur during the initial phase of treatment with GnRH agonist. They are usually asymptomatic and nonfunctional.
***Very few cases of hypersensitivity reactions have been reported from post-marketing use.

The table below lists adverse events from post-marketing experience which cannot be estimated from the available data.

Table 2: Listing of AEs/ADRs reported from post-marketing experience in patients who received DECAPEPTYL 100 micrograms daily.

MedDRA System organ class	Frequency not known
Immune system disorders	Allergic reaction
Eye disorders	Vision blurred, visual impairment
Gastrointestinal disorders	Abdominal discomfort
Skin and subcutaneous tissue disorders	Urticaria, angioedema
Reproductive system and breast disorders	Ovarian enlargement
General disorders and administration site conditions	Injection site reaction (HLT)[I], drug ineffective

[I] The injection site reactions High Level Term (HLT) includes several injection site reaction terms that have been reported in post-marketing experience with triptorelin acetate.

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Studies MFK/IVF/0399E and FE999906 CS003 listed in **Table 3** were not prospectively designed to test triptorelin and AEs reported during stimulation may not reflect events associated with triptorelin.

Table 3: Treatment-Emergent AEs reported by at least 1% of the IVF/ICSI patients receiving DECAPEPTYL 100 micrograms daily in studies MFK/IVF/0399E and FE999906 CS003.

MedDRA Preferred Term	MFK/IVF/0399E n (%)		FE999906 CS003 n (%)	
	Onset During Down-regulation with triptorelin N=113	Onset During Stimulation N=113	Onset During Down-regulation with triptorelin N=781	Onset During Stimulation N=731
Headache	30 (27%)	31 (27%)	29 (4%)	36 (5%)
Dizziness	5 (4%)	6 (5%)		
Dysmenorrhoea	7 (6%)	2 (2%)	20 (3%)	
Vaginal Haemorrhage		2 (2%)		176 (24%)
Pelvic Pain				43 (6%)
Leukorrhoea		2 (2%)		

MedDRA Preferred Term	MFK/IVF/0399E n (%)		FE999906 CS003 n (%)	
	Onset During Down-regulation with triptorelin N=113	Onset During Stimulation N=113	Onset During Down-regulation with triptorelin N=781	Onset During Stimulation N=731
Application site disorders **All events** **Inj. Site Inflammation** **Inj. Site Pain** **Inj. Site Bruising** **Inj. Site Reaction**	 16 (14%) 13 (12%) 5 (4%) -- 2 (2%)	 20 (18%) 11 (10%) 8 (7%) 3 (3%) 3 (3%)		
Abdominal Pain	10 (9%)	17 (15%)		
Abdominal Distension				18 (2%)
Nausea	6 (5%)	11 (10%)		20 (3%)
Vomiting	3 (3%)			
Diarrhoea		2 (2%)		
Ovarian Cyst			10 (1%)	8 (1%)
Abortion Spontaneous				48 (7%)
Abortion Missed				15 (2%)
OHSS				23 (3%)
Adnexa Uteri Pain				12 (2%)
Upper Resp. Tract Infection	4 (4%)	4 (4%)		
Dyspnoea	2 (2%)			
Influenza-like Symptoms		3 (3%)		
Pharyngitis		3 (3%)		
Rhinitis		2 (2%)		
Fatigue	3 (3%)	4 (4%)		
Hot Flushes	2 (2%)			
Malaise		2 (2%)		
Back Pain	3 (3%)	3 (3%)		
Flushing	4 (4%)			
Post Procedural Pain				26 (4%)
Post-operative Pain		3 (3%)		

Post-marketing experience

This post-marketing safety summary provides information on the daily dosing of triptorelin, formulation for ART indication, covering the period 1 January 1989 to 31 December 2013.

A total of 91 adverse drug reaction cases have been reported to Ferring Pharmaceuticals in this period. Out of 91 cases, 45 were reported as serious (14 unlisted and 29 listed) and 46 cases non-serious.

Among the serious unlisted cases reported, there were two cases of OHSS reported in which other serious unlisted events were also reported (cerebral artery thrombosis, and ovarian haemorrhage). Also two serious unlisted cases each comprising ectopic pregnancy and paraesthesia were reported. In the remaining 10 serious unlisted cases, the following preferred terms were reported: pulmonary oedema, drug ineffective, pelvic inflammatory disease, exposure during pregnancy, genital pain, bundle branch block, hyperemesis gravidarum, cerebellar syndrome,

thrombocytopenia, and blood pressure increased.

In three cases the subjects were exposed to daily dosing of triptorelin during the pregnancy. In two of these cases, the outcome of the pregnancy was a normal healthy baby was delivered. One case was confounded by the co-suspected drug clomipramine, used for obsessive compulsive disorder during pregnancy. The baby was discovered to have Down's syndrome and an abortion was chosen.

In general, injection site reactions (inflammation and pain) were reported as non-serious, mild and reversible.

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.

4.9 OVERDOSE

Overdose in humans may result in a prolonged duration of action. In the case of overdose, DECAPEPTYL treatment should be (temporarily) discontinued. No adverse reaction has been reported as a consequence of overdose.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Pharmacotherapeutic group: Gonadotropin releasing hormone analogues, ATC code: L02AE04
Triptorelin, a gonadotropin releasing hormone (GnRH) agonist, inhibits gonadotropin secretion when given continuously and in therapeutic doses. After the administration of triptorelin there is an initial and transient increase in circulating follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels (flare-up). Continued administration of triptorelin then results in decreased FSH and LH secretion with a consequent marked reduction in gonadal hormone production. The exact duration of action of DECAPEPTYL has not been established, but pituitary suppression is maintained for at least 6 days after stopping administration. After discontinuation of DECAPEPTYL, a further drop in circulating LH levels should be expected, with LH levels returning to baseline after approximately 2 weeks.
DECAPEPTYL-induced down-regulation of the pituitary can prevent the LH surge and thereby prevent premature ovulation and/or follicular luteinisation. The adoption of a down-regulation agent is intended to reduce the cycle cancellation rate and improve the pregnancy rate in assisted reproductive technology (ART) cycles.

Clinical trials

MFK/IVF/0399E and FE999906 CS003 were large randomised, multi-centre studies comparing highly purified-human menopausal gonadotrophin (HP-hMG) and recombinant follicle stimulating hormone (rFSH) in patients (18-38 years) undergoing controlled ovarian stimulation for *in-vitro* fertilisation/intracytoplasmic sperm injection (IVF/ICSI) following the long GnRH agonist protocol starting in the mid-luteal phase (refer to **Table 4**). These clinical studies were not prospectively designed to test the efficacy of triptorelin.

In MFK/IVF/0399E, several GnRH agonists were used for down-regulation. A total of 781 patients started down-regulation, of whom 117 were given DECAPEPTYL 100 micrograms. Adequate down-regulation was established by serum estradiol < 200 pmol/L (56 pg/mL) and no ovarian cysts.

Table 4: Summary of patient demographics for clinical trials.

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Primary Endpoint
MFK/IVF/0399E (ART)	Randomised (HP-hMG versus rFSH), open Stimulation with HP-hMG or rFSH, then individual adjustment Fixed dose of 225 IU HP-hMG or rFSH for 5 days. Investigator adjusted until criteria were met or patient withdrawn for poor response; for a maximum of 20 days.	Decapeptyl 100 micrograms s.c. Decapeptyl Depot 3.75 mg (single injection) Other GnRH agonists	GnRH agonist: 781, controlled ovarian stimulation (COS): 727 Decapeptyl 100 micrograms s.c.: 117 started down regulation, 113 started down regulation with Decapeptyl 100 micrograms and underwent COH	18-38 years	Ongoing pregnancy rate
FE999906 CS003 (ART)	Randomized (HP-hMG versus rFSH) open, assessor blind Stimulation with HP-hMG or rFSH (225 IU for first 5 days, then individual adjustment)	Decapeptyl Daily 100 micrograms s.c.	Decapeptyl 100 micrograms s.c.: 781 Randomised to HP-hMG or rFSH for COH: 731	21-37 years	Ongoing pregnancy rate

In FE999906 CS003, patients (21-37 years) diagnosed with tubal or unexplained infertility, including endometriosis stage III/IV and mild male factor eligible for IVF, were enrolled. In this study, 781 patients started down-regulation and all received DECAPEPTYL 100 micrograms s.c. daily. Confirmation of down-regulation prior to randomisation to HP-hMG or rFSH was defined as menstrual bleeding and transvaginal ultrasound showing a shedded endometrium with a thickness of < 5 mm and no ovarian cysts or serum estradiol (E_2) < 50 pg/mL and no ovarian cysts.

A total of 898 patients were exposed to DECAPEPTYL 100 micrograms s.c. in these two studies. The primary endpoint in MFK/IVF/0399E and FE999906 CS003 was ongoing pregnancy rates (defined as at least one viable foetus at 10-11 weeks after embryo transfer) after one cycle. In FE999906 CS003, a strict protocol and treatment approach were implemented to minimize sources

of variation in the study, including harmonisation of concomitant fertility treatments, a pre-specified stimulation goal and homogeneity of other major pre- and post-randomisation interventions.

The treatment outcome associated with different types of GnRH agonists can be derived from MFK/IVF/00399E. Comparative data with respect to ongoing pregnancy rate are shown in **Table 5**.

Among the 113 patients who were down-regulated with DECAPEPTYL 100 micrograms and underwent COH, the ongoing pregnancy rate was 24% (27/113). By comparison, the ongoing pregnancy rate was 21% for patients down-regulated with DECAPEPTYL Depot 3.75 mg, and 25% for those who had used other GnRH agonists (daily or depot). Although this study was not designed to draw comparisons between different down-regulation agents, these results suggest that the ongoing pregnancy rate when DECAPEPTYL 100 micrograms s.c. daily was used is not different from the rates observed with the use of other GnRH agonists.

Table 5: Comparative data with respect to ongoing pregnancy rate.

Ongoing pregnancy rate by GnRH Agonist (MFK/IVF/0399E)			
	DECAPEPTYL DAILY 100 micrograms	DECAPEPTYL Depot 3.75 mg	Other GnRH agonists[1]
Ongoing pregnancy rate	24% (27/113)	21% (96/466)	25% (37/148)
[1] buserelin, leuprolide, goserelin, nafarelin			

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pharmacokinetic data suggest that after s.c. administration of the product, the systemic bioavailability of triptorelin is close to 100%. Following a single dose of triptorelin 250 micrograms s.c. in healthy male subjects (n=4), the mean maximum plasma concentration of triptorelin was 5.68 (range: 4.76 to 7.14) ng/mL (n=4). Maximum plasma concentrations were reached approximately 45 minutes after s.c. administration.

Distribution

Following an intravenous (i.v.) bolus injection of 500 micrograms triptorelin to 19 female subjects, the drug is distributed and eliminated according to a 3-compartment model and the corresponding half-lives are 3.2 (range: 1.4 to 10.9) minutes, 46.1 (range: 20.2 to 138.1) minutes and 5.1 (range: 2.5 to 13.8) hours. The estimated volume of distribution at steady-state of triptorelin was 28.9 (range: 13.1 to 78.6) L. Protein binding has not been investigated.

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 either completely degraded within tissue or rapidly further degraded in plasma or cleared by the kidneys. Following i.v. bolus injection of 500 micrograms triptorelin to 19 female subjects the drug was distributed and eliminated according to a 3-compartment model. The mean terminal half-life was 5.1 (range: 2.5 to 13.8) hours. Average total clearance was estimated to 107 (range: 89 to 188) mL/min. Urinary excretion was investigated in 8 of the female subjects. Renal

clearance over 24 hours was on average 25.3 (range: 5.3 to 45.4) mL/min. The mean percentage of the dose recovered in urine over the 24 hours was 16.7 (range: 3.4 to 34.6) %.

Special populations
Patients with renal and liver impairment have also been studied after i.v. administration. This pharmacokinetic data is only available in male volunteers. Compared to young healthy adult males, mean triptorelin clearance was reduced by 43% in subjects with moderate renal impairment (mean creatinine clearance 40 mL/min), by 58% in subjects with severe renal impairment (mean creatinine clearance 8.9 mL/min) and by 73% in subjects with combined hepatic impairment (Child Pugh score 5-9) and a lower mean creatinine clearance (90 mL/min) than that of young healthy adult males.

These clinical studies indicate a risk of accumulation of triptorelin in patients with severe liver and renal impairment. However, the risk of accumulation appears to be small, given that the triptorelin terminal half-life is approximately 8 hours in these patients.

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
In vitro tests for gene mutations in bacterial and mammalian cells and for chromosomal damage *in vitro* and *in vivo* (mouse micronucleus test) revealed no genotoxic activity for triptorelin.

Carcinogenicity
Carcinogenicity studies were conducted in mice (18 months) and rats (up to 23 months) with microparticles containing triptorelin, administered once monthly by intramuscular injection. No carcinogenic effect was observed in mice with treatment at up to 6000 micrograms/kg/month (equivalent to 214 micrograms/kg/day), estimated to yield almost 4 times the clinical exposure at the maximum recommended human dose. In rats, pituitary adenomas and carcinomas were increased with treatment at all dose levels tested (≥120 micrograms/kg/month; equivalent to 4.3 micrograms/kg/day, and estimated to yield less than a sixth of clinical exposure at the maximum recommended human dose). Rats are recognised to be particularly sensitive to such effects of luteinising hormone-releasing hormone (LHRH) analogues compared with other species. The clinical relevance of the finding is unknown but considered likely to be low.

Life-long exposure to triptorelin had no carcinogenic effect on mice but caused species specific pituitary adenomas in rats. The rat finding was considered to be related to a rodent specific pharmacological effect of triptorelin and of no relevance to humans; no signs of mutagenicity, clastogenicity or carcinogenicity were recorded for triptorelin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to **Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION**

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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original package, to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Each 1 mL syringe of DECAPEPTYL contains a solution of 100 micrograms of triptorelin acetate equivalent to 95.6 micrograms triptorelin free base.

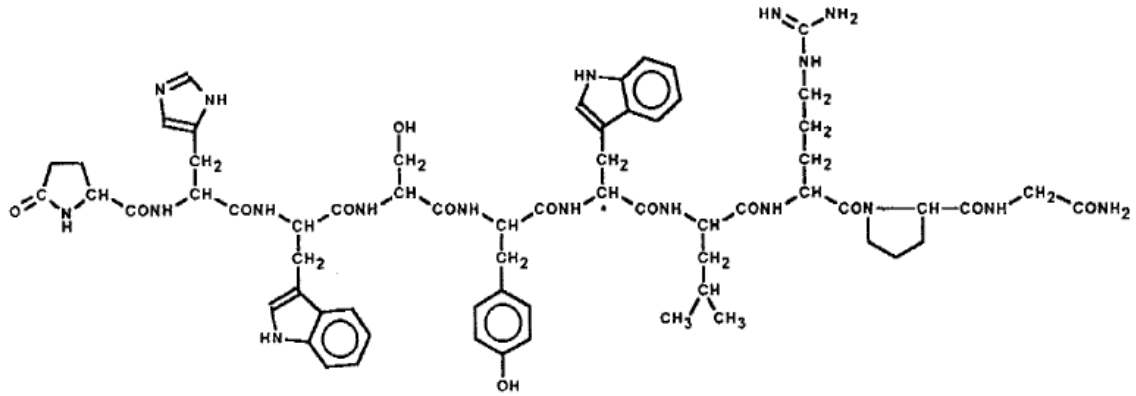
1 mL solution in a pre-filled syringe (glass) with plunger stopper (chlorobutyl rubber), plunger rod (polystyrene), integrated needle and rigid needle shield in pack size of 7 pre-filled syringes.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure:
L-pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolyl-glycinamide, acetate salt



CH_3COOH
* D-configuration. All other optically active amino acids are in L-configuration

Molecular formula:
$C_{64}H_{82}N_{18}O_{13}$ (free base)
$C_{64}H_{82}N_{18}O_{13}\ C_2H_4O_2$ (triptorelin acetate)

Molecular weight:
1311.5 (net) + 60.1 (acetate) = 1371.6 (triptorelin acetate)

CAS number:
160296-12-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8 SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

Toll Free: 1800 337 746

9 DATE OF FIRST APPROVAL

4 March 2015

10 DATE OF REVISION

6 August 2024

For the most current approved PI, please refer to https://www.ebs.tga.gov.au/ or http://www.ferring.com.au/

Summary table of changes

Section Changed	Summary of new information
4.4	Mood changes and depression – updated to specify this is a class effect of GnRH agonists. Bone loss – updated to include treatment duration without add-back therapy.
4.8	Rare (frequency classification of adverse event) has been added. **Adverse Event frequency were updated as follows:** Hypersensitivity – Frequency not known to Uncommon; Nausea – Uncommon to Common; Ovarian cyst – Uncommon to Common; Injection site reactions – Uncommon to Frequency not known **The following Adverse Events have been added:** Mood altered, depression, fear, vision blurred, visual impairment, dyspnoea, abdominal discomfort, hyperhidrosis, rash, pruritus, blister, urticaria, angioedema, musculoskeletal pain, breast pain, vaginal discharge, ovarian

	enlargement, injection site erythema, injection site discolouration, injection site irritation, cyst
5.3	Carcinogenicity information for humans, mice and rats has been updated.
All	Minor editorial changes