Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Decapeptyl SR, 3 mg powder and solvent for suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains the quantity of triptorelin (as triptorelin acetate) to ensure that the minimum quantity injected is 3 mg.

A 2 mL ampoule of solvent for suspension is provided in each pack.
Once reconstituted, 1 ml of the suspension contains 1.5 mg triptorelin at a minimum.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

A sterile, white to off-white, lyophilised powder which, when reconstituted as directed with the clear, colourless, sterile liquid, yields a sterile suspension for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prostatic carcinoma
In the management of advanced prostatic carcinoma

Uterine fibromyomas
Treatment of uterine fibromyomas

Endometriosis
Genital and extragenital endometriosis

Breast cancer
As adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in women at high risk of recurrence who are confirmed as pre-menopausal after completion of chemotherapy (see Sections 4.3, 4.4, 4.8 and 5.1),

Female infertility
Complementary treatment in association with the gonadotropins (hMG, FSH and hCG) in the course of ovulation induction in view of *in-vitro* fertilisation and embryo transfer (I.V.F.E.T.).

4.2 Posology and method of administration

Prostatic cancer:
Male adults only:
One intramuscular injection of Decapeptyl SR (3 mg) every 28 days.
No special requirements are needed for the elderly.
In patients with metastatic castration-resistant prostate cancer not surgically castrated, receiving a GnRH agonist such as triptorelin and eligible to a treatment by abiraterone acetate, an inhibitor of androgen biosynthesis or enzalutamide, an inhibitor of signalling pathway of androgen receptors, the treatment by a GnRH agonist must be continued.

Uterine fibromyomas:

The treatment must be initiated in the first five days of the cycle. The recommended dose is one intramuscular injection every 28 days.
Injection schedule: this depends on the change in volume of the fibromyomas, assessed by ultrasonography.
In principle, fibromyomas should be treated for at least 4 months and for a maximum of 6 months. A second course of treatment by Decapeptyl SR or by other GnRH analogues should not be undertaken.

Breast cancer
One intramuscular injection every 4 weeks in combination with tamoxifen or an aromatase inhibitor. Triptorelin should be commenced after completion of chemotherapy, once pre-menopausal status has been confirmed (see section 4.4). The treatment with triptorelin must be initiated at least 6-8 weeks before starting aromatase inhibitor treatment. A minimum of two injections of triptorelin (with an interval of 4 weeks between injections) should be administered before commencement of aromatase inhibitor treatment.
During treatment with an aromatase inhibitor, triptorelin must not be interrupted in order to avoid rebound increases in circulating oestrogens in premenopausal women.
The recommended treatment duration for adjuvant treatment in combination with other hormonotherapy is up to 5 years.
Since Decapeptyl SR 3.75 mg is a suspension of microparticles, inadvertent intravascular injection must be strictly avoided.

Endometriosis:
The treatment must be initiated in the first five days of the cycle.
Injection schedule: one intramuscular injection of Decapeptyl SR every 28 days.
Duration of treatment: this depends on the initial severity of endometriosis and the change in clinical manifestations (functional and anatomical) during treatment.
In principle, endometriosis should be treated for at least 4 months and for a maximum of 6 months.
A second course of treatment by Decapeptyl SR or by other GnRH analogues should not be undertaken.
In patients treated with GnRH analogues for endometriosis, the addition of an add-back therapy (ABT - an estrogen and progestogen) has been shown to reduce bone mineral density loss and vasomotor symptoms. Therefore, if appropriate, ABT should be co-administered with GnRH analogue taking into account the risks and benefits of each treatment.

Female infertility:
One intramuscular injection of Decapeptyl SR administered on the second day of the cycle. In general, the stimulation by gonadotropins should be performed when the blood level of oestrogens are less than 50 pg/ml (usually around the 15th day of the cycle).

4.3 Contraindications

Hypersensitivity to GnRH (gonadotropin releasing hormone), its analogues or to any of the excipients listed in section 6.1 (see section 4.8 Undesirable effects).
Pregnancy and lactation
In the pre-menopausal breast cancer setting: Initiation of aromatase inhibitor treatment before adequate ovarian suppression with triptorelin has been achieved (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

The use of GnRH agonists may cause a reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonate in combination with a GnRH agonist may reduce bone mineral loss. No specific data is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticosteroids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Particular caution is therefore necessary since reduction in bone mineral density is likely to be more detrimental in these patients. Treatment with Decapeptyl SR should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risk following a very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density.

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

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.

There is an increased risk of 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.

This medicinal product contains less than 1 mmol of sodium (23 mg) per dose i.e. essentially 'sodium-free'.

In men

Prostate cancer

Initially, Decapeptyl SR, like other GnRH agonists, 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 their prostate cancer (tumour flare) and 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 orchidectomy (surgical castration) should be considered. Careful monitoring is indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastasis, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

After surgical castration, Decapeptyl SR does not induce any further decrease in serum testosterone levels.

Long-term androgen deprivation either by bilateral orchidectomy or administration of GnRH agonists is associated with increased risk of bone loss and may lead to osteoporosis and increased risk of bone fracture.

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) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Decapeptyl SR.

In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance, fatty liver) and an increased risk of cardiovascular disease during androgen deprivation therapy. However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and during androgen deprivation therapy.

Administration of triptorelin in therapeutic doses result 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 GnRH agonists may therefore be misleading.

In women

It should be confirmed that the patient is not pregnant before prescription of Decapeptyl SR.

The use of GnRH agonists is likely to cause reduction in bone mineral density averaging 1% per month during a six-month treatment period. Every 10% reduction in bone mineral density is linked with about a two to three times increased fracture risk.

No specific data are available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abusers, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Since reduction in bone mineral density is likely to be more detrimental in these patients, treatment with triptorelin should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risk following a very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density.

Endometriosis and Uterine Fibromyomas

GnRH agonist is not recommended for patients under the age of 18 years. Careful attention should be given to adolescent and young women (specially less than 16 years of age) who may not have reached maximum bone density.

In patients treated with GnRH analogues for endometriosis, the addition of ABT (an estrogen and progestogen) has been shown to reduce mineral density loss and vasomotor symptoms (see 'Posology and Method of Administration' section 4.2 for further information).

Used at the recommended dose, Decapeptyl SR causes constant hypogonadotropic amenorrhoea. If vaginal haemorrhage occurs after the first month, plasma oestradiol levels should be measured and if levels are below 50 pg/ml, possible organic lesions should be investigated.
After withdrawal of treatment, ovarian function resumes and ovulation occurs approximately 2 months after the last injection. A non-hormonal method of contraception should be used throughout treatment including for 1 month after the duration of the last injection.

Since menses should stop during Decapeptyl SR treatment, the patient should be instructed to notify her physician if regular menstruation persists.

It is recommended that during treatment of uterine fibroids, the size of the fibroid is determined regularly. There have been a few reports of bleeding in patients with submucous fibroids following GnRH analogue therapy. Typically, the bleeding has occurred 6 - 10 weeks after the initiation of therapy.

Breast cancer
In order to ensure adequate ovarian suppression in premenopausal women, treatment with triptorelin should be administered for at least 6-8 weeks prior to commencement of an aromatase inhibitor and monthly triptorelin injections should be administered on schedule and without interruption throughout aromatase inhibitor treatment.

Women who are premenopausal at breast cancer diagnosis and who become amenorrhoeic following chemotherapy may or may not have continued oestrogen production from the ovaries. Irrespective of menstrual status, pre-menopausal status should be confirmed following chemotherapy and before commencement of triptorelin, by blood concentrations of oestradiol and FSH within the reference ranges for pre-menopausal women, in order to avoid unnecessary treatment with triptorelin in the event of a chemotherapy-induced menopause. Following commencement of triptorelin, it is important to confirm adequate ovarian suppression (gonadotrophin analogue- induced menopause) by serial assessment of circulating FSH, and oestradiol if this subset of women is to be considered for therapy with an aromatase inhibitor in accordance with current clinical practice recommendations. Accordingly, ovarian suppression should be confirmed by low blood concentrations of FSH and oestradiol prior to starting aromatase inhibitor treatmentand measurements should berepeated every three months duringcombination therapy with triptorelin and an aromatase inhibitor. This is to avoid aromatase inhibitor-induced rebound increase in circulating oestrogen, with consequential implications for breast cancer. Of note, circulating FSH levels are lowered in response to gonadotrophin analogue-induced ovarian suppression (induced menopause), unlike in a natural menopause where FSH levels are elevated.

Triptorelin, when used as adjuvant therapy in combination with tamoxifen or an aromatase inhibitor, is associated with a high risk of osteoporosis. Osteoporosis has been reported with a higher frequency following the use of triptorelin in combination with an aromatase inhibitor than in combination with tamoxifen (39% vs 25%).

Bone mineral density should be assessed before starting treatment with triptorelin, especially in women who have multiple risk factors for osteoporosis. These patients should be closely monitored and treatment for, or prophylaxis of, osteoporosis should be initiated when appropriate.

Treatment of premenopausal women with endocrine responsive early stage breast cancer with triptorelin in combination with tamoxifen or an aromatase inhibitor should follow a careful individual appraisal of the risks and benefits.

Patients who have discontinued triptorelin treatment should also discontinue aromatase inhibitors within 1 month of the last triptorelin administration (1 month formulation).

The risk of musculoskeletal disorders (including joint or musculoskeletal pain) when triptorelin is used in combination with either an aromatase inhibitor or tamoxifen is approximately 89% with the AI and approximately 76% with tamoxifen.

Hypertension was reported as a targeted adverse event at a very common frequency with triptorelin in combination with either exemestane or tamoxifen (see section 4.8). Premenopausal women with breast cancer receiving triptorelin in combination with either exemestane or tamoxifen should have regular monitoring of cardiovascular risk factors and blood pressure.

Hyperglycaemia and diabetes were reported as targeted adverse events at a common frequency with triptorelin in combination with either exemestane or tamoxifen (see section 4.8). Premenopausal women with breast cancer receiving triptorelin in combination with either exemestane or tamoxifen should have regular monitoring of risk factors for diabetes with blood glucose monitoring on a regular basis and appropriate anti-diabetic treatment initiated, if appropriate, according to national guidelines.

Depression occurred in approximately 50% of patients treated with triptorelin in combination with either tamoxifen or exemestane in all treatment groups in the TEXT and SOFT studies, but less than 5% of patients had severe depression (grade 3-4). Patients should be informed accordingly and treated as appropriate if symptoms occur. Patients with known depression or depression history should be carefully monitored during therapy.

Particular attention should also be paid to the exemestane and tamoxifen prescribing information for relevant safety information when administered in combination with triptorelin.

Chemotherapy can induce temporary amenorrhoea or a permanent loss of ovarian function due to cytotoxic damage of gonadal tissue. Retention of pre-menopausal status following completion of chemotherapy should be confirmed as recommended by clinical guidelines by blood concentrations of oestradiol and FSH within the reference ranges for pre-menopausal women.

Female infertility
The induction of ovulation should be monitored under rigorous medical supervision with strict and regular biological and clinical control by fast plasma oestrogen assay and ultrasonography. As with other GnRH analogues there have been reports of ovarian hyperstimulation syndrome (OHSS) associated with the use of triptorelin in combination with gonadotropins.
In cases of excessive ovarian response, interruption of the stimulation cycle by stopping the injections of gonadotropins is recommended.
The increase in the follicular retrieval induced by injection of Decapeptyl SR when associated with gonadotropins may be great in some predisposed patients and particularly in cases of polycystic ovarian disease. The ovarian response to the triptorelin-gonadotropin treatment may differ with the same doses from one patient to another, and in certain cases, from one cycle to another in the same patient.
In patients with renal or hepatic impairment, triptorelin has a mean terminal half life of 7-8 hours compared to 3-5 hours in healthy subjects. Despite this prolonged exposure, triptorelin is not expected to be present in circulation at the time of embryo transfer.

4.5 Interaction with other medicinal products and other forms of interaction

Hyperprolactinemic drugs should not be prescribed concomitantly as they reduce the level of GnRH receptors in the pituitary.

When Decapeptyl SR is co-administered with drugs affecting pituitary secretion of gonadotropins, caution should be exercised and it is recommended that the patient's hormonal status be supervised.

Prostate cancer
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Decapeptyl SR 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).

4.6 Fertility, pregnancy and lactation

Pregnancy
Decapeptyl SR should not be used during pregnancy since concurrent use of GnRH agonists is associated with a theoretical risk of abortion or foetal abnormality. Prior to treatment, potentially fertile women should be examined carefully to exclude pregnancy. Non-hormonal methods of contraception should be employed during therapy until menses resume.

Breastfeeding
Decapeptyl SR should not be used during lactation.

Fertility

Pregnancy should be excluded before triptorelin is used for fertilisation treatment. When Decapeptyl SR is used in this setting, there is no clinical evidence to suggest a causal connection between Decapeptyl SR and any subsequent abnormalities of oocyte development or pregnancy or outcome.

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 and visual disturbances (being possible undesirable effects of treatment), or resulting from the underlying disease.

4.8 Undesirable effects

Clinical trials experience
General tolerance in Men (see section 4.4)
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, more than 90% of the patients included in clinical trials reported adverse events, and often the causality is difficult to assess. 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. These effects included hot flushes and decreased libido.

With the exception of immuno-allergic (rare) and injection site (< 5%) reactions, all adverse events are known to be related to testosterone changes.

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

The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); not known; (cannot be estimated from the available data).

System Organ Class	**Very common ≥ 1/10**	**Common ≥1/100 - <1/10**	**Uncommon ≥1/1,000 - <1/100**	**Rare ≥1/10,000 - <1/1,000**	**Additional post-marketing AEs Frequency not known**
Infections and infestations				Nasopharyngitis	
Blood and lymphatic system disorders			Thrombocytosis		
Immune system disorders		Hypersensitivity		Anaphylactic reaction	Anaphylactic shock
Endocrine disorders					Pituitary apoplexy**
Metabolism and nutrition disorders			Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite		
Psychiatric disorders	Libido decreased	Depression* Loss of libido Mood change*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	
Eye disorders			Visual impairment	Abnormal sensation in eye Visual disturbance	
Ear and			Tinnitus		

labyrinth disorders			Vertigo		
Cardiac Disorders			Palpitations		QT prolongation* (see sections 4.4 and 4.5)
Vascular disorders	Hot flush	Hypertension		Hypotension	
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	Orthopnoea	
Gastrointestinal disorders		Dry mouth Nausea	Abdominal pain Constipation Diarrhoea Vomiting	Abdominal distension Dysgeusia Flatulence	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne Alopecia Erythema Pruritus Rash Urticaria	Blister Purpura	Angioneurotic oedema
Musculoskeletal and connective tissue disorders	Back pain	Musculoskeletal pain Pain in extremity	Arthralgia Bone pain Muscle cramp Muscular weakness Myalgia	Joint stiffness Joint swelling Musculoskeletal stiffness Osteoarthritis	
Renal and urinary disorders			Nocturia Urinary retention		Urinary incontinence
Reproductive system and breast disorders	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic pain	Breast pain Gynaecomastia Testicular atrophy Testicular pain		
General disorders and administration site conditions	Asthenia	Injection site reaction (including erythema, inflammation and pain) Oedema	Lethargy Oedema peripheral Pain Rigors Somnolence	Chest pain Dysstasia Influenza like illness Pyrexia	Malaise
Investigations		Weight increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased Blood pressure increased Blood urea increased Gamma-glutamyl transferase	Blood alkaline phosphatase increased	

			increased Weight decreased		

* This frequency is based on class-effect frequencies common for all GnRH agonists
**Reported following initial administration in patients with pituitary adenoma

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. These symptoms are transient and usually disappear in one to two weeks.

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).

Patients receiving long-term treatment by GnRH analogue in combination with radiation therapy may have more side effects, mostly gastrointestinal and related to radiotherapy.

The use of 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.

General tolerance in Women (see section 4.4)
As a consequence of decreased oestrogen levels, the most commonly reported adverse events (expected in 10% of women or more) were headache, libido decreased, sleep disorder, mood altered, dyspareunia, dysmenorrhoea, genital haemorrhage, ovarian hyperstimulation syndrome, ovarian hypertrophy pelvic pain, abdominal pain, vulvovaginal dryness, hyperhidrosis, hot flushes and asthenia.

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.

The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1000 to < 1/100); not known; (cannot be estimated from the available data).

System Organ Class	**Very common ≥ 1/10**	**Common ≥1/100 - <1/10**	**Uncommon ≥1/1000 - <1/100**	**Additional post-marketing AEs Frequency not known**
Immune system disorders		Hypersensitivity		Anaphylactic shock
Endocrine disorders				Pituitary apoplexy***
Metabolism and nutrition disorders			Decreased appetite Fluid retention	
Psychiatric disorders	Libido decreased Mood disorder Sleep disorder (including insomnia)	Depression* Nervousness	Affect lability Anxiety Depression** Disorientation	Confusional state
Nervous system disorders	Headache	Dizziness	Dysgeusia Hypoesthesia Syncope Memory impairment Disturbance in attention Paraesthesia	

			Tremor	
Eye disorders			Dry eye Visual Impairment	Visual disturbance
Ear and labyrinth disorders			Vertigo	
Cardiac Disorders			Palpitations	
Vascular disorders	Hot flushes			Hypertension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	
Gastrointestinal disorders		Abdominal pain Abdominal discomfort Nausea	Abdominal distension Dry mouth Flatulence Mouth ulceration Vomiting	Diarrhoea
Skin and subcutaneous tissue disorders	Acne Hyperhidrosis Seborrhoea		Alopecia Dry skin Hirsutism Onychoclasis Pruritus Rash	Angioneurotic oedema Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia Muscle spasms Pain in extremities	Back pain Myalgia	Muscular weakness
Reproductive system and breast disorders	Breast disorder Dyspareunia Genital bleeding (including vaginal bleeding withdrawal bleed) Ovarian hyperstimulation syndrome Ovarian hypertrophy Pelvic pain Vulvovaginal dryness	Breast pain	Coital bleeding Cystocele Menstrual disorder (including dysmenorrhoea, metrorrhagia and menorrhagia) Ovarian cyst Vaginal discharge	Amenorrhoea
General disorders and administration site conditions	Asthenia	Injection site reaction (including pain, swelling, erythema and inflammation) Oedema peripheral		Malaise Pyrexia
Investigations		Weight increased	Weight decreased	Blood alkaline phosphatase increased Blood pressure increased

*Long term use: This frequency is based on class-effect frequencies common for all GnRH agonists
** Short term use: This frequency is based on class-effect frequencies common for all GnRH agonists
*** Reported following initial administration in patients with pituitary adenoma

At the beginning of treatment, the symptoms of endometriosis including pelvic pain and dysmenorrhoea may be very commonly exacerbated (≥ 10%) during the initial transient increase in plasma oestradiol levels. These symptoms are transient and usually disappear in one or two weeks.

Genital haemorrhage including menorrhagia, metrorrhagia may occur in the month following the first injection.

When used to treat infertility, the combination with gonadotropins may result in ovarian hyperstimulation syndrome. Ovarian hypertrophy, pelvic and/or abdominal pain may be observed.

Breast Cancer
The most commonly observed adverse reactions associated with triptorelin treatment for up to 5 years in combination with either tamoxifen or an aromatase inhibitor in the TEXT and SOFT studies were hot flushes, musculoskeletal disorder, fatigue, insomnia, hyperhidrosis, vulvovaginal dryness and depression.

The frequencies of the adverse reactions reported with triptorelin in combination with tamoxifen (N = 2325) or exemestane (N = 2318) are shown in the following table. The classifications are as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000).

System Organ Classes	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10,000 to <1/1000**
Cardiac disorders			Myocardial Ischaemia	QT prolongation
Endocrine disorders		Diabetes mellitus (glucose intolerance) Hyperglycaemia		
Gastrointestinal disorders	Nausea			
General disorders and administration site conditions	Fatigue	Injection site reaction		
Immune system disorders		Hypersensitivity		
Musculoskeletal and connective tissue disorders	Musculoskeletal disorder Osteoporosis	Fracture		
Nervous system disorders			Cerebral ischaemia Central nervous system haemorrhage	
Psychiatric disorders	Insomnia Libido decreased Depression			
Renal and urinary disorders	Urinary incontinence			
Reproductive system and breast disorders	Dyspareunia Vulvovaginal dryness			
Skin and subcutaneous tissue disorders	Hyperhidrosis			
Vascular disorders	Hot flushes Hypertension	Embolism		

The ADRs identified above should be used in addition to the triptorelin ADRs identified in men and women in tables above to fully describe the ADR profile for the use of OFS in combination with either exemestane or tamoxifen.

Osteoporosis has been reported at a higher frequency with the use of triptorelin in combination with exemestane than in combination with tamoxifen (39% versus 25%) (see section 4.4).

Musculoskeletal disorder and fractures were also more commonly reported in combination with exemestane than in combination with tamoxifen (89% versus 76% and 6.8% versus 5.2%, respectively).

Hypertension has been reported as a targeted adverse event at a very common frequency with triptorelin in combination with either exemestane or tamoxifen (23% and 22% respectively).

Hyperglycaemia and diabetes have been reported as targeted adverse events at a common frequency with triptorelin in combination with either exemestane or tamoxifen (hyperglycaemia: 2.6% and 3.4% respectively; diabetes: 2.3% and 2.3% respectively).

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

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance: Website: www.hpra.ie.

4.9 Overdose

If overdose occurs, symptomatic management is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormones and related agents,
ATC code: L02A EO4

Triptorelin is a synthetic decapeptide (D-Trp6 GnRH) analogue of natural GnRH. Studies in animals and man have shown that continued administration of triptorelin exerts, after a short initial stimulation, an inhibitory effect on the gonadotropin secretion with consequent suppression of testicular and ovarian functions.

Prostatic cancer
The first administration of Decapeptyl SR stimulates the release of pituitary gonadotropins with a resultant increase in peripheral circulating levels of testosterone and dihydrotestosterone. Prolonged administration (over 7 days) leads to a suppression of gonadotropins and a fall in plasma testosterone to castrate levels after approximately 20 days and which continues for as long as the product is administered.

A transient increase in acid phosphatases may be observed in men at the beginning of treatment.
In patients with metastatic castration-resistant prostate cancer, clinical studies have shown the benefit from the addition of androgen biosynthesis inhibitors, such as abiraterone acetate to GnRH analogues, such as triptorelin.

Uterine fibromyomas
The suppression of oestrogen secretion produces a significant reduction of the volume of the uterine fibromyomas.

Endometriosis
Continued administration of Decapeptyl SR induces suppression of the oestrogen secretion and thus enables resting of ectopic endometrial tissue.

Female infertility

The administration of Decapeptyl SR induces an initial phase of gonadotropin stimulation (FSH and LH) followed by an inhibition phase. The treatment ensures suppression of the intercurrent LH peak enabling enhanced folliculogenesis and increased follicular retrieval and as a consequence, a better rate of pregnancy per cycle.

Breast cancer

Clinical studies performed in premenopausal women with endocrine responsive early stage breast cancer have been conducted with triptorelin in order to suppress ovarian oestradiol secretion, the main source of oestrogens. Based on studies performed in healthy women and women with endometriosis, the effect of triptorelin is achieved 3 4 weeks after administration.

Two phase 3 studies (SOFT and TEXT) have explored the 5-year benefit of ovarian function suppression (OFS) in combination with tamoxifen (T) or an aromatase inhibitor (exemestane - E) in premenopausal women with endocrine responsive early stage breast cancer.

Triptorelin was the main treatment used to achieve OFS (91.0% of randomised subjects in the SOFT study, and 100% in the TEXT study). The remaining 9% of women in the SOFT study had bilateral oophorectomy or bilateral ovarian irradiation.

SOFT study results

The SOFT study was designed to answer the question of the added value of OFS to tamoxifen as adjuvant treatment in premenopausal women with endocrine responsive early stage breast cancer.
A total of 3047 women were analysed (1015 women in the T+OFS, 1018 women in the T alone and 1014 womenin the E+OFS arm).

At a median follow-up of 67 months (5.6 years), treatment with T+OFS non-significantly reduced the hazard of a Disease Free Survival (DFS) event versus T alone (HR=0.83; 95% CI, 0.66 to 1.04; p=0.10). The estimated 5-year DFS was 86.6% (95% CI, 84.2% to 88.7%) among women assigned to T+OFS compared with 84.7% (95% CI, 82.2% to 86.9%) for womenassigned to T alone.

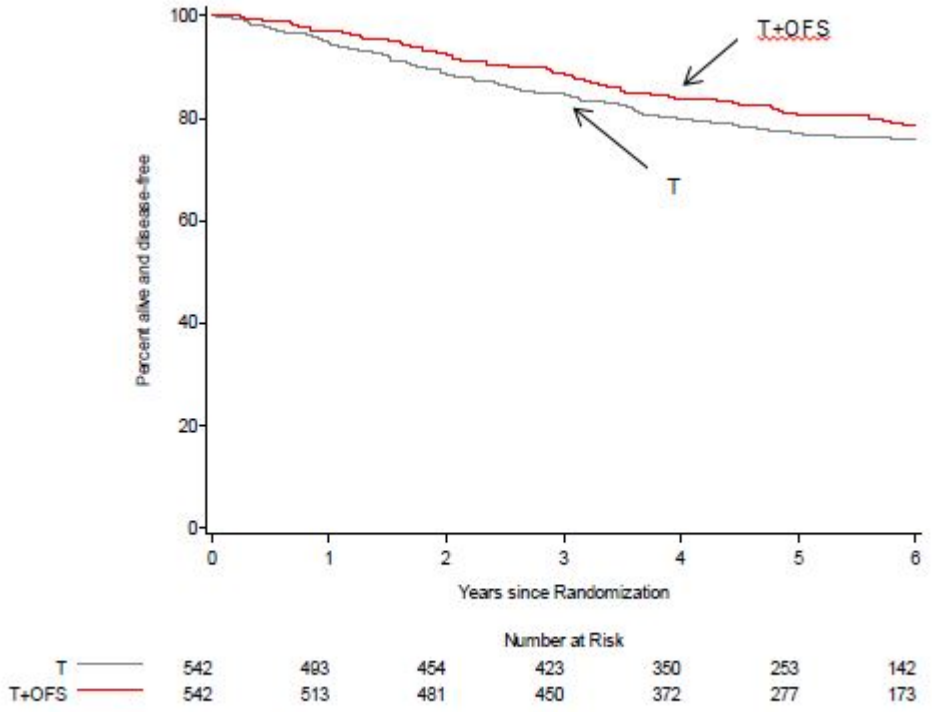
However, after adjustment for prespecified covariates in the multivariate Cox model, women assigned treatment with T+OFS had a significantly reduced hazard of a DFS event compared with women assigned T alone, with a reduction of 22% (HR=0.78; 95% CI, 0.62 to 0.98; p=0.03).

Women assigned treatment with T+OFS had a non-significantly reduced hazard of a breast cancer event compared with women assigned T alone (HR=0.81; 95% CI, 0.63 to 1.03; p=0.09). The estimated 5-year Breast Cancer Free Interval (BCFI) was 88.4% (95% CI, 86.1% to 90.3%) for women assigned treatment with T+OFS compared with 86.4% (95% CI, 84.0% to 88.5%) for women assigned T alone.

However, after adjusting for pre-specified covariates in the multivariable Cox model, women assigned T+OFS had a significantly reduced hazard of a BCFI event compared with women assigned T with a reduction of 25% (HR=0.75; 95% CI, 0.59 to 0.96; p=0.02).

The absolute risk benefit is higher in women who received adjuvant chemotherapy. The DFS rate at 5 years for women who received adjuvant chemotherapy was 80.7% in the T + OFS arm and 77.1% in the T arm only (HR=0.82; 95% CI, 0.64 to 1.07) with an absolute benefit of 3.6% for T+OFS.

Kaplan-Meir Estimates of DFS in women who received prior chemotherapy



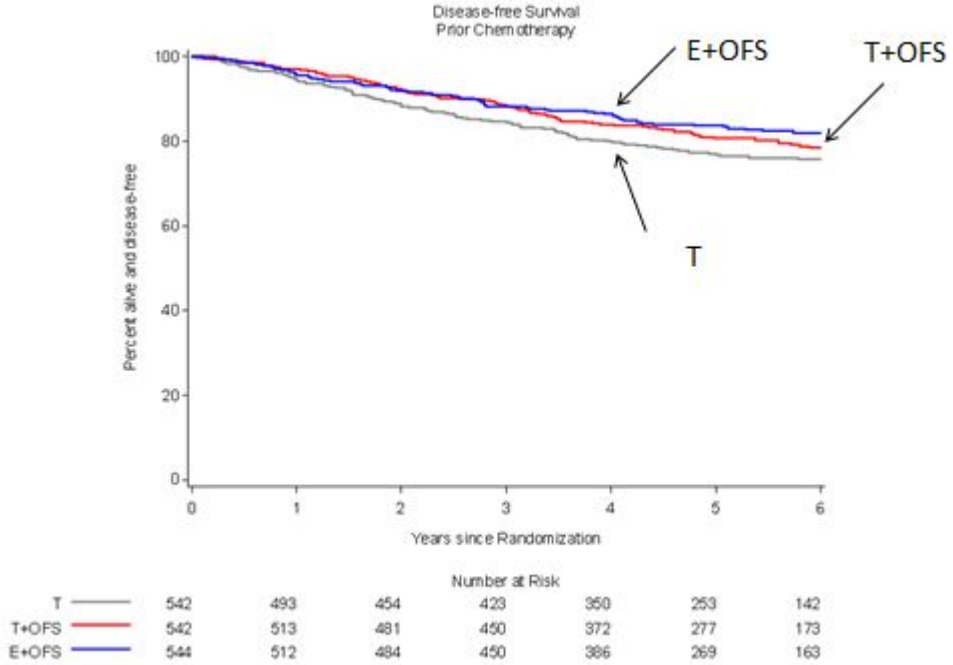
In particular, the benefit of adding OFS was apparent for 5-year DFS in a post-hoc analysis for the subgroup of women less than 40 years old (HR=0.74; 95% CI, 0.53, 1.03) with an absolute benefit of 4.4% for T+OFS compared to T alone.
In the SOFT study, subjects assigned E+OFS had a statistically significantly reduced hazard of a DFS event, as compared with subjects assigned T alone (HR=0.68, 95% CI, 0.53 to 0.86). The estimated 5-year DFS rate was 89.0% (95% CI, 86.8% to 90.9%) among subjects assigned to E+OFS as compared with 84.7% (95% CI, 82.2% to 86.9%) among subjects assigned T alone.

Subjects assigned E+OFS had a statistically significantly reduced hazard of a breast cancer event as compared with subjects assigned T alone (HR=0.64; 95% CI, 0.49 to 0.83). The estimated 5-year BCFI was 90.9% (95% CI, 88.9% to 92.6%) among subjects assigned E+OFS compared with 86.4% (95% CI, 84.0% to 88.5%) among subjects assigned T alone.

Subjects assigned E+OFS had a statistically significantly reduced hazard of a distant recurrence as compared with subjects assigned T alone (HR=0.71; 95% CI, 0.52 to 0.96). The estimated 5-year Distant Recurrence Free Interval (DRFI) was 93.0% (95% CI, 91.2% to 94.5%) among subjects assigned E+OFS compared with 90.7% (95% CI, 88.6% to 92.4%).

The absolute benefit is higher in women who received adjuvant chemotherapy. The DFS rate at 5 years for women who received adjuvant chemotherapy was 83.8% in the E + OFS arm and 77.1% in the T arm only (HR=0.70, 95%CI, 0.53 to 0.92) with an absolute benefit of 6.7% for E+OFS.

Kaplan-Meir Estimates of DFS in women who received prior chemotherapy



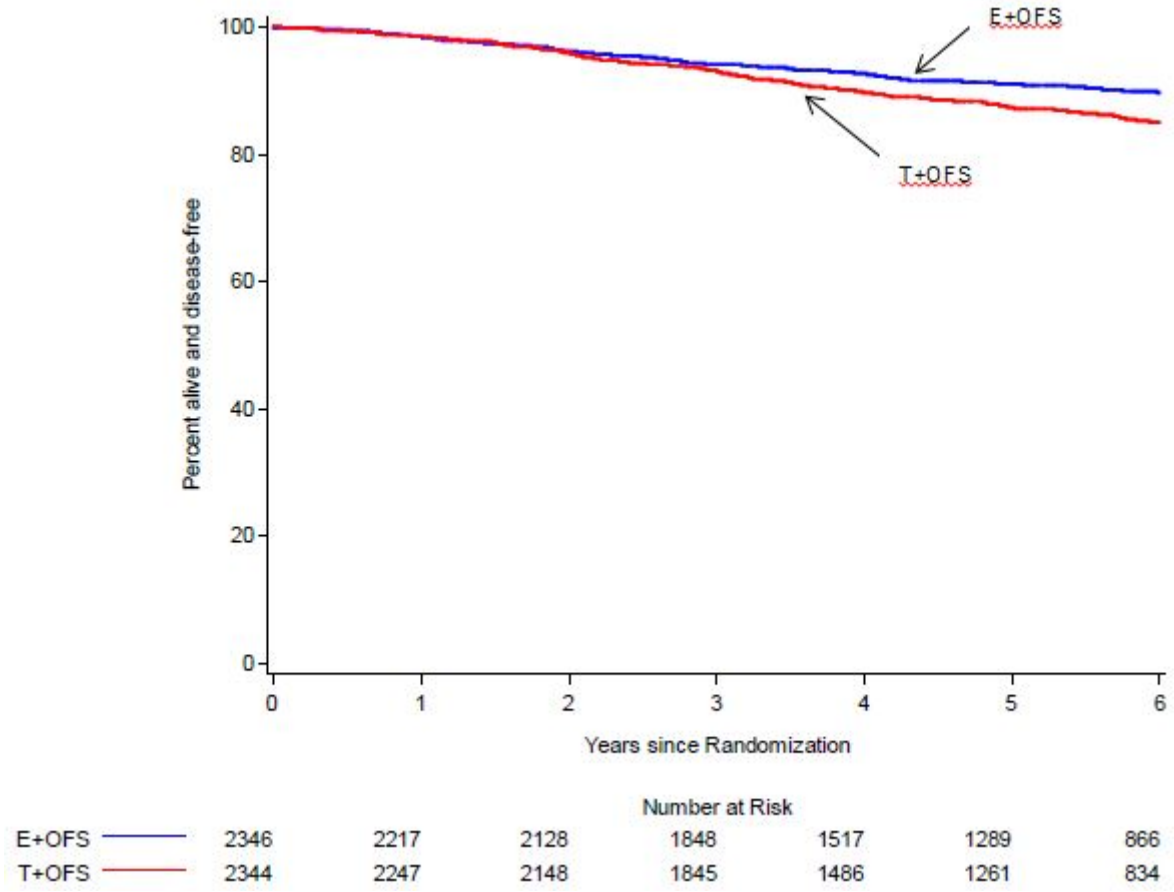
In the 3 arms SOFT study, women who received chemotherapy had a higher proportion of high risk clinical criteria of recurrence: 49.3% below age < 40, 56.9% with lymph nodes positive, 47.0% with breast tumour size > 2 cm and 33.7% with tumour grade 3.

Combined SOFT and TEXT study results

The primary objective of TEXT study was to evaluate the role of aromatase inhibitors (exemestane) in women treated with OFS compared with T+OFS including all women from SOFT and TEXT studies. A total of 4690 women were analyzed: 2346 women in the E+OFS arm and 2344 women in the T+OFS arm.

At a median follow-up of 68 months (5.7 years), treatment with E+OFS statistically significantly reduced the hazard of a DFS event versus T+OFS (HR=0.72; 95% CI, 0.60 to 0.86; p=0.0002). The estimated 5-year DFS was 91.1% (95% CI, 89.7% to 92.3%) for women assigned to E+OFS compared with 87.3% (95% CI, 85.7% to 88.7%) for womenassigned T+OFS.

Kaplan-Meir Estimates of DFS OFS+E vs OFS +T



Women assigned E+OFS had a statistically significantly reduced hazard of a breast cancer event compared with women assigned T+OFS (HR=0.66; 95% CI, 0.55 to 0.80; P<0.0001). The estimated 5-year BCFI was improved at 92.8% (95% CI, 91.6% to 93.9%) for women assigned E+OFS compared with 88.8% (95% CI, 87.3% to 90.1%) for women assigned T+OFS.

5.2 Pharmacokinetic properties

In men:
Following intramuscular injection an initial phase of release of the active principle present on the surface of the microspheres is observed, followed by regular release of triptorelin at a mean rate of 46.6 ± 7.1 µg/day. The microsphere suspension bioavailability is approximately 53% at one month.

In women
After intramuscular injection of Decapeptyl in endometriosis and uterine fibroid women the maximum blood level of triptorelin is obtained between 2 to 6 hours after injection, the peak value reached is 11 ng/ml. There was no evidence of accumulation of the product after 6 months of monthly injections. Trough plasma concentrations are maintained between 0.1 and 0.2 ng/ml. The bioavailability of the sustained release product is approximately 50%.

These data observed in endometriosis and uterine fibroma patients can be extrapolated to breast cancer patients as it is not expected that the disease has an impact on the prolonged release properties of the product.

5.3 Preclinical safety data

Preclinical findings were only those related to the expected pharmacological activity of triptorelin, namely down-regulation of the hypothalamic-pituitary-gonadal axis. These included atrophy of the testes and genital tract, with resultant suppression of spermatogenesis, together with decreased weight of the prostate gland. These findings were largely reversible within the recovery period. Resorption of the microspheres is complete within 40 to 45 days following intramuscular injection in rats.

Standard mutagenicity testing revealed no mutagenic activity of triptorelin. Triptorelin is not mutagenic in vitro or in vivo. In mice, no oncogenic effect has been shown with triptorelin at doses up to 6000 µg/kg after 18 months of treatment. A

23-month carcinogenicity study in rats has shown an almost 100% incidence of benign pituitary tumours at each dose level, leading to premature death. The increased incidence in 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

Powder
D,L Lactide- glycolide copolymer

Mannitol
Carmellose sodium
Polysorbate 80

Solvent for suspension
Mannitol
Water for Injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Powder: 3 years.
Solvent: 5 years.

The product should be used immediately after opening/reconstitution.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Powder for suspension for injection:
Type I, clear, slightly tinted glass vial (4 ml)

Solvent for suspension for injection:
Type I, clear glass ampoule (2 ml)

Box containing 1 vial and 1 ampoule with 1 syringe and 2 needles.

6.6 Special precautions for disposal and other handling

The suspension for injection must be reconstituted using an aseptic technique and only using the ampoule of solvent for injection.

The instructions for reconstitution hereafter and in the leaflet must be strictly followed.

The solvent should be drawn into the syringe provided using the reconstitution needle (20 G, without safety device) and transferred to the vial containing the powder. The suspension should be reconstituted by swirling the vial gently from side to side for long enough until a homogeneous, milky suspension is formed. Do not invert the vial.

It is important to check there is no unsuspended powder in the vial. The suspension obtained should then be drawn back into the syringe, without inverting the vial. The reconstitution needle should then be changed and the injection needle (20 G, with safety device) used to administer the product.

As the product is a suspension, the injection should be administered immediately after reconstitution to prevent precipitation.

For single use only.

Used needles, any unused suspension or other waste materials should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ipsen Pharmaceuticals Limited
Blanchardstown Industrial Park
Blanchardstown
Dublin 15
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0869/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 December 1989

Date of last renewal: 05 December 2009

10 DATE OF REVISION OF THE TEXT

August 2023