SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Decapeptyl Depot 3.75 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 3.75 mg triptorelin embonate equivalent to 3.75 mg triptorelin.
1 ml of reconstituted suspension contains 1.875 mg triptorelin after dissolution in 2 ml solvent.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection

The powder is white to off-white powder and the solvent is a clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Decapeptyl Depot 3.75 mg is indicated for lowering of sexual hormone;
treatment of advanced hormone-dependent prostatic cancer

and for the treatment of central precocious puberty.
As adjuvant treatment in combination with tamoxifen or an aromatase inhibitor of hormone receptor-positive early stage breast cancer in women at high risk of recurrence and who are confirmed as pre-menopausal after completion of chemotherapy (see sections 4.3, 4.4, 4.8 and 5.1) and in men at high risk of recurrence.

4.2 Posology and method of administration

Posology

Decapeptyl Depot 3.75 mg The usual dosage is one intramuscular injection of Decapeptyl Depot 3.75mg every month under medical supervision.

Central Precocious Puberty: Initially, 3.75 mg on days 0, 14, 28 and then 3.75 mg every 28 days. If the effect is insufficient, injections may be given every 21 days. Dosing should be based on body weight. Children weighing less than 20 kg are injected with 1.875 mg (half-dose), children between 20 and 30 kg receive 2.5 mg (2/3 dose), and children weighing more than 30 kg are injected with 3.75 mg (full dose).Treatment should be stopped if a bone maturation of older than 12 years in girls and older than 13 years in boys has been achieved.

Breast cancer

The content from a vial, equal 3.75 mg triptorelin, is injected intramuscularly once a month (every 4 weeks) in combination with tamoxifen or an aromatase inhibitor (AI).
Triptorelin should be commenced after completion of chemotherapy, once pre-menopausal status has been confirmed.

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 to avoid rebound increases in circulating oestrogens in pre-menopausal women.
The recommended treatment duration for adjuvant treatment in combination with other hormonotherapy is up to 5 years.

Treatment monitoring

Men: For treatment monitoring, PSA and testosterone in serum should be determined. After an initial increase in serum testosterone reaches castration level after 2-4 weeks and remains as long as the treatment continues. Transient increase in the amount of acidic phosphatase occurs sometimes in the early stages but has generally returned to normal or near normal values during the 4th week.
Female: Pregnancy should be excluded before starting treatment.

Special dosage recommendations

*Elderly patients***:** The dose does not have to be adapted to age.

The medicine is not indicated for post-menopausal women.

Patients with renal or hepatic impairment
No dosage adjustment is necessary for patients with renal or hepatic impairment.

Method of administration
Precautions to be taken before handling or administrating the medicinal product
As with other medicinal products administered by injection, the injection site should be varied periodically.
Since Decapeptyl depot 3.75mg is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.
The injection of Decapeptyl depot 3.75mg is administered by health care professionals.
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to GnRH, its analogues or to any of the excipients listed in section 6.1 (see also section 4.8).

Pregnancy and breastfeeding.

In the pre-menopausal breast cancer setting: Initiation of aromatase inhibitor before adequate ovarian suppression with triptorelin has been achieved (see sections 4.2 and 4.4).

Prostate cancer

Decapeptyl Depot 3.75mg should not be administered if the tumour is not hormone-dependent or after surgical castration.

In patients with spinal cord compression caused by metastases of their prostate cancer.

4.4 Special warnings and precautions for use

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 a 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).

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 appropriately if symptoms occur. Patients with known depression should be monitored closely during therapy.

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

Prostate cancer

Initially triptorelin, 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 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 (surgical castration) 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.

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.
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 profile including the potential for Torsades de pointes prior to initiating Decapeptyl depot.

In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance), or 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 adequately monitored during androgen deprivation therapy.

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 GnRH analogues may therefore be misleading.

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

Reduction in bone mineral density

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 abuses, 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.

Breast cancer
In order to ensure adequate ovarian suppression in pre-menopausal 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 pre-menopausal 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 follicle-stimulating hormone (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 assessments 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 treatment and measurements should be repeated every three months during this combination therapy with triptorelin and an aromatase inhibitor. This is to avoid aromatase inhibitor-induced rebound increase in circulating oestrogen, with consequential implications for the 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 pre-menopausal women with hormone receptor-positive 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 aromatase inhibitor and approximately 76% with tamoxifen.

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). Pre-menopausal

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.

Endometriosis
Used at the recommended dose, triptorelin causes constant hypogonadotropic amenorrhoea. If genital 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 last injection.
Since menstruation should stop during triptorelin treatment, the patient should be instructed to notify her physician if regular menstruation persists.

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

In girl's 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. In most girls, regular menses will start on average one year after ending the therapy.
Pseudo-precocious puberty (gonadal or adrenal tumour or hyperplasia) and gonadotropin-independent precocious puberty (testicular toxicosis, familial Leydig cell hyperplasia) should be precluded.

Slipped capital femoral epiphysis can be seen after withdrawal of GnRH 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.

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

> *Children*: The chronological age at the beginning of therapy should be under 9 years in girls and under 10 years in boys.

4.5 Interaction with other medicinal products and other forms of interaction

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

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Decapeptyl depot with medicinal products known to prolong the QT interval or medicinal products able to induce Torsades 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
Pregnancy should be excluded before Decapeptyl depot is prescribed.
Triptorelin 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.

Breast-feeding
Triptorelin must not be used during breast-feeding.

Fertility
Animal studies have shown effects on reproductive parameters (see section 5.3 Preclinical safety data).

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

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, erectile dysfunction 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 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 (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	**Additional post-marketing AE Frequency not known**
Infections *and infestations*		Urinary tract infections		Nasopharyngitis	
Blood and lymphatic system disorders			Thrombocytosis		
Immune system disorders		Hyper-sensitivity		Anaphylactic reaction	Anaphylactic shock
Metabolism and nutrition disorders			Anorexia, Diabetes mellitus, Gout, Hyperlipidaemia, Increased appetite		
Psychiatric disorders	Decreased libido	mood changes*, loss of libido, depression*	Insomnia, Irritability	Confusional state, Decreased activity, Euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	headache, dizziness,	praesthesia	Memory impairment *	
Eye disorders			Visual impairment	visual fdisturbances , Abnormal sensation in eye,	
Ear *and labyrinth disorders*			Tinnitus, vertigo		
Cardiovascula					

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	**Additional post-marketing AE Frequency not known**
r disorders			Palpitations		QT prolongation* (see sections 4.4 and 4.5)
Vascular disorders	Hot flushes	Hypertension		Hypotension	
Respiratory *thoracic and mediastinal disorders*			Dyspnoea, Epistaxis	Orthopnoea	
Gastrointestinal disorders		nausea, Dry mouth,	Abdominal pain, Constipation, Diarrhoea, vomiting	Abdominal distension, Dysgeusia flatulence	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne, Alopecia, Erythema, Pruritus, Rash, Urticaria	Blisters, Purpura	Angioneurotic oedema
Musculoskeletal *and connective tissue* disorders	Back pain	Musculoskeletal pain, Pain in extremities	Muscle weakness Arthralgia, Bone pain, Muscle cramp, 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	Pelvic plain	Gynaecomastia, Breast pain, Testicular atrophy, testicular pain		

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	**Additional post-marketing AE Frequency not known**
	failure, ejaculation disorder)				
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 increase	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	

* This frequency is based on class-effect frequencies common for all GnRH agonists

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 metastases 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 Special warnings and special precautions for use).

The use of GnRH agonists, to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increase the risk of bone fracture.

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

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 (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

System Organ Class	**Very Common AEs**	**Common AEs**	**Uncommon AEs**	**Additional post-marketing AEs** Frequency not known
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and nutrition disorders			Loss of 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	

System Organ Class	**Very Common AEs**	**Common AEs**	**Uncommon AEs**	**Additional post-marketing AEs** Frequency not known
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		Nausea, Abdominal pain, Abdominal discomfort	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, Tiredness		Pyrexia, Malaise
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

At the beginning of treatment, the symptoms of endometriosis including pelvic pain, dysmenorrhea may be exacerbated very commonly (≥ 10%) during the initial transient increase in plasma oestradiol levels. These symptoms are transient and usually disappear in one or two weeks. Genital hemorrhage including menorrhagia, metrorrhagia may occur in the month following the first injection.

Long-term use of GnRH analogues may lead to bone loss which is a risk factor of osteoporosis.

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 flush, 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**	**Common**	**Uncommon**	**Rare**
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 flush, 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 with a higher frequency with the use of triptorelin in combination with exemestane than in the 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).

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

General tolerance in children (see section 4.4)
The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

System Organ Class	**Very Common AEs**	**Common AEs**	**Uncommon**	**Additional post-marketing AEs Frequency not known**
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and nutrition disorders			Obesity	
Psychiatric disorders			Mood altered	Affect lability, Depression, Nervousness
Nervous system disorders		Headache		
Eye disorders			Vision impairment	Visual disturbance
Vascular disorders		Hot flushes		Hypertension
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Gastrointestinal disorders		Abdominal pain	Vomiting, Constipation, Nausea	
Skin and subcutaneous tissue disorders		Acne	Pruritus, Rash, Urticaria	Angioneurotic oedema
Musculoskeletal and connective tissue disorders			Neck pain	Myalgia
Reproductive system and breast disorders	Vaginal bleeding (including haemorrhage, withdrawal bleed, uterine haemorrhage, vaginal discharge, vaginal bleeding including spotting)		Breast pain	
General disorders and administration site conditions		Injection site reaction (including pain, erythema and inflammation)	Malaise	
Investigations		Weight increased		Blood prolactin increased, Blood pressure increased

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

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

If overdosage occurs, symptomatic management is indicated.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

gonadotropin releasing hormone analogues.

ATC code: L02AE04

Mechanism **of action** *and pharmacodynamic effects*

The active substance in Decapeptyl depot, triptorelin, a GnRH agonist which is structurally similar to natural GnRH (Gonadorelin). Triptorelin is different from the endogenous hormone by amino acid glycine in the 6-position has been replaced by D-tryptophan. This change of the GnRH molecule increases, and gives a more long-lasting effect on, the release of LH and FSH from the pituitary gland than natural GnRH.

Initially, triptorelin gives a transient increase in LH and FSH release, with accompanying elevated testosterone, oestrogen and progesterone levels in plasma. Subsequently inhibited the release of gonadotropin which leads to testosterone or oestrogen in the plasma drops to castration-and prepubescent and postmenopausal values after 2-4 weeks.

Subsequent injections of Decapeptyl depot do not give rise to any initial stimulation of the pituitary and gonads. The effects of triptorelin are reversible.

In treated women, menstruation returns 2-3 months after the last injection of Decapeptyl depot.

Clinical efficacy and safety

Prostate cancer

Clinical efficacy

Prostate cancer
Following a single intramuscular injection of Decapeptyl depot 3.75 mg to healthy male volunteers, serum testosterone levels first increased by peaking on day 4 and thereafter declined to low levels by 4 weeks. By week 8, following this single injection, low levels of testosterone were no longer maintained. A similar serum testosterone profile was observed in patients with advanced prostate cancer when injected intramuscularly with triptorelin embonate and following the second injection testosterone levels were maintained within the castrate range.

Breast cancer
Clinical studies performed in pre-menopausal women with hormone receptor-positive early stage breast cancer have been conducted with triptorelin in order to suppress oestradiol ovarian 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 pre-menopausal women with hormone receptor-positive 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.

The SOFT study included subjects following breast surgery who remained pre-menopausal after the completion of adjuvant or neoadjuvant chemotherapy and pre-menopausal women who had not received chemotherapy and for whom adjuvant T alone was considered suitable treatment. Subjects were randomised to receive E+OFS, T+OFS or T alone. In the TEXT study women were included following breast surgery and randomised to treatment with T+OFS or E+OFS; those receiving chemotherapy commenced it concurrently with the GnRH analogue after randomization. Efficacy in both studies was measured using the primary endpoint of 5-year disease-free survival (DFS) and secondary endpoints included breast cancer-free interval (BCFI), distant recurrence-free interval (DRFI) and overall survival (OS).

SOFT study results

The SOFT study was designed to answer the question of the added value of OFS to tamoxifen as adjuvant treatment of pre-menopausal women with hormone receptor-positive early stage breast cancer.

This OFS question analysis compared DFS between subjects randomly assigned to T+OFS versus T alone. At a median follow-up of 67 months (5.6 years), DFS events were reported for 299/2033 subjects (14.7%) in the intention-to-treat population (ITT).

Overall, 53.3% of subjects received prior chemotherapy (i.e. subjects who tended to have a high risk of recurrence of breast cancer). The absolute difference at 5 years was more notable among subjects who received prior chemotherapy: DFS, 80.7% (T+OFS) versus 77.1% (T alone) (Table 1).

Table 1 OFS Question: 67-month Efficacy Results for Subjects who Received Prior Chemotherapy (ITT Population)

Efficacy Endpoints	T Alone N=542		T+OFS N=542		T Alone vs T+OFS Hazard Ratio (95% CI)
	Events	Event-free rates (%)	Events	Event-free rates (%)	
DFS[a]	122	77.1	107	80.7	0.82 (0.64 to 1.07)
BCFI	116	78.0	97	82.5	0.78 (0.60 to 1.02)
DRFI	90	83.6	82	84.8	0.87 (0.64 to 1.17)
OS[b]	57	90.9	39	94.5	0.64 (0.42 to 0.96)

BCFI=breast cancer-free interval, CI=confidence interval, DFS=disease-free survival, DRFI=distant recurrence-free interval, ITT=intention-to-treat, OFS=ovarian function suppression, OS=overall survival, T=tamoxifen

a Disease-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer, or death from any cause

b Overall survival data immature at 67-months.

Combined SOFT and TEXT study results

The TEXT study was designed to evaluate the role of aromatase inhibitors (AIs) (exemestane) in the adjuvant treatment of pre-menopausal women with hormone receptor-positive early stage breast cancer

who are treated with OFS. The AI Question analysis combined the TEXT and SOFT studies and compared DFS between subjects randomly assigned to E+OFS versus T+OFS.

At a median follow-up of 68 months (5.7 years), DFS events were reported for 514/4690 subjects (11.0%) in the ITT population. Overall, the estimated 5-year DFS was improved at 91.1% (95% CI, 89.7% to 92.3%) among subjects assigned E+OFS versus 87.3% (95% CI, 85.7% to 88.7%) among subjects assigned T+OFS (HR=0.717; 95% CI, 0.602 to 0.855; p=0.0002). Table 2 shows the efficacy results for subjects who received prior chemotherapy in the AI analysis.

Table 2 AI Question: 68-month Efficacy Results for Subjects who Received Prior Chemotherapy (ITT Population)

Efficacy Endpoints	E+OFS N=544		T+OFS N=543		Hazard Ratio E+OFS vs T+OFS (95% CI)
	Events	Event-free rates (%)	Events	Event-free rates (%)	
DFS[a]	81	84.3	98	80.6	0.838 (0.625 to 1.125)
BCFI	72	86.1	90	82.2	0.818 (0.600 to 1.116)
DRFI	61	88.0	77	84.6	0.808 (0.577 to 1.131)
OS[b]	46	91.8	35	94.1	1.387 (0.894 to 2.154)

AI=aromatase inhibitor, BCFI=breast cancer-free interval, CI=confidence interval, DFS=disease-free survival, E=exemestane, DRFI=distant recurrence-free interval, ITT=intention-to-treat, OFS=ovarian function suppression, OS=overall survival, T=tamoxifen

a Disease-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer, or death from any cause.

b Overall survival data immature at 68-months.

An updated analysis after a median follow-up of 8 years has confirmed the positive benefit/risk profile of 5-year triptorelin treatment.

5.2. Pharmacokinetic properties

In Decapeptyl depot triptorelin is in the form of biodegradable micro particles suspended in an aqueous phase, is injected intramuscularly and is a depot with the gradual release of the active ingredient. Maximum plasma concentrations are reached within one hour after administration and fall rapidly to steady state. Therapeutic plasma concentrations well above the level needed to maintain the pharmacodynamic effect are maintained over the dosing interval.

After one intramuscular injection of Decapeptyl depot 3.75 mg in healthy pre-menopausal women, maximum triptorelin concentrations were observed around 2 hours post-dose and the geometric mean value of C_{max} was 18.5 ng/mL.

The time to oestradiol suppression was around 4.2 days (geometric mean) and the duration of E2 suppression was around 26.7 days (geometric mean). Despite a quite high inter-subject variability, globally, 5 days after the IM injection of Decapeptyl Depot 3.75 mg, an oestradiol suppression was observed for around 30 days.

5.3 Preclinical safety data

In experiments with rats, high doses of triptorelin given rise to early fetal death or resorption. It is unclear what role these effects may have for humans.

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients

1 vial of powder for injection contains: poly(d,l-lactide-co-glycolide), mannitol, carmellose sodium, polysorbate 80

1 ampoule of 2 ml solvent contains: Water for injection

6.2. Incompatibilities

Decapeptyl depot powder for injection should only be mixed in the pack for the solvent.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

Use immediately after reconstitution.

6.4. Special precautions for storage

Store bellow 25ºC.

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5. Nature and contents of container

1 vial with powder containing 3.75mg triptorelin

1 ampoule with solvent containing 2 ml water for injection.

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) and transferred to the vial containing the powder. The vial 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) 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 injections, used needles, any unused suspension or other waste material should be disposed of in accordance with local requirements.

The suspension for injection should be prepared immediatelly before use.

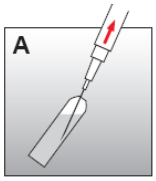
Preparation for injection.

Two needles are provided in the box:

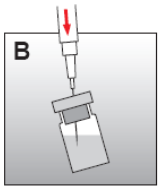
- The reconstitution needle
- The injection needle

- Tap any solution that may be present in the tip of the ampoule back into the main reservoir of the solvent ampoule.
- Screw the reconstitution needle onto the syringe (do not remove the needle guard at this point!)
- Break open the solvent ampoule (breakpoint facing your body).

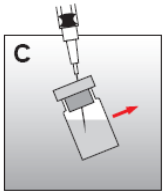
- Remove the needle guard from the reconstitution needle and draw up all the solvent into the syringe (Fig.A).



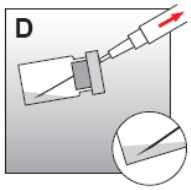
- Put aside the syringe containing the solvent.
- Take out the vial containing the powder. Tap any powder which has accumalated at the top of the vial back to the bottom of the vial.
- Remove the plastic cap from the top of the vial.
- Pick up the syringe containing the solvent again and insert the needle thorogh the rubber stopper of the vial and slowly inject the solvent so that it flows down the edge of the vial over a wide area (Fig.B).



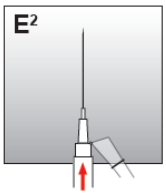
- Pull up the needle to above the level of the liquid and gently swirl the vial to produce a homogeneous, milky suspension for injection (Fig.C). Make sure there is no powder left in the vial, and if nessesary, continue swirling the vial until the powder has completely disappeared. N.B.: Do not mix the suspension by repeatedly filling and emptying the syringe!



- Then draw up all of the suspension for injection into the syringe (Fig.D).



- Remove the reconstitution needle. Firmly screw the injection needle onto the syringe (screw it on tightly). Only touch the colored hub.
- .
- Remove the needle guard from the injection needle.
- Expel any air from the syringe (Fig.E2).



Injection

Inject the suspension for injection relatively rapidly and in a steady and uninterrupted manner into the muscles.

After use

- Dispose the needle in a designated sharps container.

For single use only. Any unused suspension must be discared

7. **Name of manufacturer:**
DEBIOPHARM RESEARCH & MANUFACTURING S.A, SWITZERLAND

8. Name of registration holder: Ferring pharmaceuticals LTD, 8 Hashita Street, Industrial Park, Caesarea 308800, Israel.

9. Registration number: 132-28-28860

This leaflet was revised in May 2021 according to MOH guidelines.