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

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 cases of pre-menopausal breast cancer: Initiation of aromatase inhibitor 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 lead to reduced bone density. In men, preliminary data indicate that the use of a bisphosphonate in combination with a GnRH agonist may reduce the loss of bone mineral. Special precautions are necessary in patients with additional risk factors for osteoporosis (e.g., chronic alcohol abuse, smoking, long-term therapy with drugs that reduce bone mineral density, e.g., anticonvulsants or corticoids, family history of osteoporosis, malnutrition).

In rare cases, treatment with GnRH agonists can lead to the discovery of a previously undetected gonadotroph cell pituitary adenoma. These patients may present with a pituitary apoplexy with sudden headache, vomiting, visual impairment and ophthalmoplegia.
There is an increased risk of depression (which may be severe) for patients who are being treated with GnRH agonists, such as triptorelin. The patients should be informed of this and treated appropriately if symptoms arise. Patients known to have depression should be monitored closely during therapy.

Caution should be exercised when intramuscular injections are administered in patients treated with anticoagulants, because of a potential risk of haematomas at the injection site.

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

This medicinal product contains less than 1 mmol (23 mg) sodium per injection vial, i.e., it is practically “sodium free”.

Prostate cancer

Like other GnRH agonists, triptorelin initially causes a transient increase in serum testosterone levels. In isolated cases this can lead to temporarily worsened disease symptoms during the first weeks of treatment.

To counteract this initial increase in serum testosterone and worsening of clinical symptoms, additional administration of a suitable antiandrogen should be considered at the start of treatment.

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

As with other GnRH agonists, isolated cases of medullary compression or urinary tract obstruction have been observed. If medullary compression or impaired renal function develops, conventional treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy (surgical castration) should be considered. There should be close monitoring in the first weeks of treatment, especially of patients suffering from vertebral metastases, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

Triptorelin does not result in any further reduction in serum testosterone concentration following surgical castration.

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 fractures.

Androgen deprivation therapy may prolong the QT interval.

For patients with QT prolongation in their medical history of with risk factors for QT prolongation, and in patients on concomitant treatment with other drugs that may prolong the QT interval (see section 4.5) prescribers should determine the benefit/risk balance including the risk of Torsades de pointes before commencing treatment with Decapeptyl depot.

In addition to this, it has been observed from epidemiological data that patients may experience metabolic changes (e.g., glucose intolerance, fatty liver), or an increased risk of cardiovascular disease during androgen deprivation therapy. Prospective data have not, however, confirmed the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients with an increased risk for metabolic or cardiovascular diseases must be investigated thoroughly before commencing treatment and followed up during androgen deprivation therapy.

Administration of triptorelin in therapeutic doses results in suppression of the pituitary gland's gonad function. Normal function is usually restored after completion of treatment. Diagnostic tests of pituitary gonadal function conducted during treatment and after completion of treatment with GnRH analogues may therefore be misleading.

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

Females

It should be confirmed that the patient is not pregnant before starting treatment with Decapeptyl depot 3.75mg.

Reduction in bone mineral density

The use of GnRH agonists entails a high probability of a reduction in bone mineral density. During a 6-month treatment period bone density can drop by approx. 1% a month. The risk of fracture increases two to three-fold for each 10% reduction in bone density.

No data are available for patients with clinically confirmed osteoporosis or risk factors for osteoporosis (e.g. chronic alcohol abuses, smoking, 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 harmful in these patients, treatment with triptorelin should be considered on an individual basis and only commenced if the benefits of treatment outweigh the risks. Additional measures to counteract a reduction in bone density should be considered.

Breast cancer

To achieve adequate ovarian function suppression in pre-menopausal women, treatment with triptorelin should be administered for at least 6-8 weeks before initiating an aromatase inhibitor, and monthly triptorelin injections should be administered on schedule and without interruption throughout aromatase inhibitor treatment.

Women who are pre-menopausal when they receive their breast cancer diagnosis and who experience amenorrhoea after chemotherapy may retain or lose continued oestrogen production from the ovaries. Regardless of menstrual status, pre-menopausal status should be established after chemotherapy care and before initiating triptorelin, by checking that the blood concentrations of oestradiol and follicle-stimulating hormone (FSH) is within the reference interval for pre-menopausal women. This is to avoid unnecessary treatment with triptorelin in the event of chemotherapy-induced menopause. After initiating triptorelin, it is important to determine adequate ovarian function suppression (gonadotrophin analogue-induced menopause) through a series of measurements of circulating FSH and oestradiol if order to decide if aromatase inhibitor treatment in line with current clinical practice may be appropriate for this subgroup of women. Ovarian function suppression should consequently be determined through low blood concentrations of FSH and oestradiol prior to starting aromatase inhibitor treatment, and measurements should be repeated every three months during combination therapy with triptorelin and an aromatase inhibitor. This is to avoid an increase in circulating oestrogen through aromatase inhibitor-induced rebound effect, with subsequent consequences for the breast cancer. Note, that the circulating FSH levels are lowered in response to gonadotrophin analogue-induced ovarian function suppression (induced menopause), unlike in a natural menopause where FSH levels are elevated.

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

Bone 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 with triptorelin in combination with tamoxifen or an aromatase inhibitor for premenopausal women with early stage hormone receptor-positive breast cancer should be monitored individually and closely by means of an assessment of the risks and benefits.

Patients who have stopped their triptorelin treatment should also stop their aromatase inhibitor treatment within a month of their final triptorelin injection (one-month formulation).

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

Hypertension, which was studied closely, was reported to be a “very common” adverse reaction both when triptorelin was combined with exemestane and when it was combined with tamoxifen (see section 4.8). Premenopausal women with breast cancer who receive triptorelin in combination with either exemestane or with tamoxifen should have regular monitoring of their cardiovascular risk factors and blood pressure.

Hyperglycaemia and diabetes were reported as especially interesting "common" adverse reactions for both triptorelin in combination with either exemestane and triptorelin in combination with tamoxifen (see section 4.8). Pre-menopausal women with breast cancer who take triptorelin in combination with either exemestane or with tamoxifen should be monitored regularly to detect any risk factors for diabetes through regular blood glucose checks and appropriate anti-diabetic treatment should be 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, although fewer than 5% of patients had severe depression (grade 3-4). Patients should be informed of this and treated appropriately if symptoms arise. Patients with known depression or depression history should be monitored closely during treatment.

Particular attention should also be paid to the prescribing information exemestane and tamoxifen with regard to the safety of their use in combination therapy with triptorelin.

Chemotherapy can induce temporary amenorrhoea or a permanent loss of ovarian function due to cytotoxic damage of gonadal tissue. The preservation of pre-menopausal status after completion of chemotherapy care should be confirmed as recommended by clinical guidelines by determining that the blood concentrations of oestradiol and FSH are within the reference values for pre-menopausal women.

Endometriosis

GnRH agonists are not recommended for patients under the age of 18. Young girls and young women (especially those under the age of 16) who may not have reached maximum bone density should be monitored closely.

The addition of ABT (an oestrogen and progestogen) in patients treated with GnRH analogues for endometriosis has been shown to reduce the loss of bone density and vasomotor symptoms (see section 4.2 "Posology and method of administration" for more information).

Triptorelin causes constant hypogonadotropic amenorrhoea when used at the recommended dose,. If vaginal bleeding occurs after the first month, the oestrogen levels should be measured and if it is below 50 pg/ml, then any link with organic pathological changes should be investigated.

When the treatment is completed, the ovaries will regain their function and ovulation should take place approximately 2 months after the final injection. Non-hormonal contraception should be used through the treatment and for 1 month after the final injection.

Since menstruation is supposed to stop during triptorelin treatment, the patient should be instructed to notify her physician if regular menstruation persists.

Central Precocious puberty

In girls, it should be confirmed that the patient is not pregnant before prescribing triptorelin. A thorough and individual assessment of the risks and benefits should be carried out when treating children with progressive brain tumors

Pseudo-precocious puberty (gonadal or adrenal tumor, or hyperplasia) and gonadotropin-independent precocious puberty (testotoxicosis, familial Leydig cell hyperplasia) should be ruled out.

In girls initial stimulation of the ovaries, followed by the treatment-induced reduction of oestrogen may lead to mild to moderate vaginal bleeding in the first month.

The traits of puberty will develop once treatment is completed. Information on future fertility is still limited.

In most girls, regular menstruation begins around a year after treatment is completed.

Bone density may decrease during GnRH treatment for central precocious puberty. However, subsequent growth of bone mass after completion of treatment is not affected; maximum bone mass in late teenage years does not appear to be affected by the treatment.

Slipping of the femoral epiphysis may occur after completion of GnRH treatment. One explanation for this could be that the low concentrations of oestrogen during treatment with GnRH agonists weakens the epiphysial plate. The increase in rate of growth that occurs after completion of treatment results in a subsequent reduction of the shearing force required to displace the epiphysis.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in paediatric patients receiving triptorelin. Patients should be warned for signs and symptoms of idiopathic

intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of triptorelin should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised when triptorelin is administered concomitantly with medicinal products that influence pituitary gonadotropin secretion monitoring of the patient's hormone status is recommended.
Since androgen deprivation treatment may prolong the QT interval, concomitant use of Decapeptyl depot with medicinal products that prolong the QT interval or with medicinal products that may induce Torsades de pointes such as class IA antiarrhythmics (e.g. quinidine, disopyramide) or class IIIA antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide) methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, Pregnancy and lactation

Pregnancy
Pregnancy should be ruled out before Decapeptyl depot is prescribed.
Triptorelin should not be used during pregnancy because concomitant use of GnRH agonists can in theory lead to a risk of spontaneous abortion or foetal abnormalities. potentially fertile women must be examined closely prior to treatment to rule out pregnancy. Non-hormonal methods of contraception should be used during treatment until menstruation returns.

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

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

4.7 Effects on ability to drive and use machines

No studies have been carried out of the ability to drive and use machines. However the ability to drive and use machines may be impaired if the patient experiences dizziness, sleepiness and visual disturbances that are possible undesirable effects of the treatment or a result of the underlying disease.

4.8 Undesirable effects

Experience from clinical trials

General tolerance in men (see section 4.4)

Since patients with locally advanced or metastatic, hormone-dependent prostate cancer are usually older and have other, for this age group, frequently occurring diseases more than 90 % of the patients included in clinical trials have reported adverse reactions, It is often difficult to determine whether there is a causal link. The most commonly reported adverse reactions related to triptorelin treatment, just as for other GnRH agonists or in cases of surgical castration, were caused by expected pharmacological effects. These effects included hot flushes and reduced libido.

With the exception of allergic reactions (rare) and injection site reactions (< 5 %), all adverse events are expected in conjunction with changes in the level of testosterone.

The following adverse reactions that have been reported are considered as at least possibly related to triptorelin treatment. Most are known to occur in conjunction with 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				nasopharyngitis	
Blood and lymphatic system disorders			thrombocytosis		Anaemia
Immune system disorders		hyper-sensitivity		Anaphylactic reaction	anaphylactic shock
Endocrine disorders					pituitary apoplexy**
Metabolism and nutrition disorders			anorexia, diabetes mellitus, gout, hyperlipidaemia, increased appetite		
Psychiatric disorders	reduced libido	mood swings*, loss of libido, depression*	insomnia, irritability	confusional state, reduced activity, euphoric mood	anxiety
Nervous system disorders	paraesthesia of the legs	headache, dizziness	praesthesia	memory impairment	
Eye disorders			visual impairment	visual disturbances, abnormal sensation in eye	
Ear and labyrinth disorders			tinnitus, vertigo		
Cardiac 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,	stomach pain, constipation, diarrhoea, vomiting	distended abdomen, taste sense altered, flatulence	
Skin and subcutaneous tissue disorders	hyperhidrosis		acne, alopecia, erythema, pruritus, , skin rash, urticaria	blisters, purpura	angioneurotic oedema

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	**Additional post-marketing AE Frequency not known**
Musculoskeletal and connective tissue disorders	back pain	musculoskeletal pain, pain in arms and legs	muscle weakness arthralgia, skeletal 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 failure to ejaculate, ejaculation disorder)	pelvic plain	gynaecomastia, breast pain, 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, difficulty standing, influenza like illness, fever	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

** Reported after initial administration in patients with a pituitary adenoma.

Triptorelin causes a transient increase in circulating testosterone levels within the first week after the initial injection of the prolonged-release formulation. As a result of the initial increase in circulating testosterone levels, a small number of patients (≤ 5 %) may experience a temporary worsened prostate cancer symptom (tumour flare), usually in the form of an increase in urinary tract symptoms (< 2%) and metastasis pain (5%), which can be treated symptomatically. These symptoms are transient and usually disappear in one to two weeks.

Isolated cases of worsened disease symptoms, either urinary tract obstruction or medullary compression caused by metastases, have been observed. For that reason, patients with vertebral metastasis and/or upper or lower urinary tract obstruction should be monitored closely the first few weeks of treatment (see section 4.4).

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

Patients receiving long-term treatment with GnRH analogues in combination with radiotherapy may get more adverse reactions, primarily gastrointestinal reactions that may stem from the radiotherapy.

General tolerance in women (see section 4.4)
As a result of reduced oestrogen levels, the most commonly reported adverse reactions (expected in 10% of women or more) were headache, libido decreased, sleep disorders, mood swings, pain on intercourse, dysmenorrhoea, genital bleeding**,** ovarian hyperstimulation syndrome, ovarian hypertrophy, pelvic pain, stomach pain, vaginal 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
Endocrine disorders				pituitary apoplexy***
Metabolism and nutrition disorders			reduced appetite, fluid retention	
Psychiatric disorders	libido decreased, mood disorders, sleep disturbances (including insomnia),	depression*, nervousness	affect lability, anxiety, depression**, disorientation	Confusional state
Nervous system disorders	headache	dizziness	taste sense altered, hypoesthesia, syncope, memory impairment,disturbances in attention paraesthesia, tremor	Convulsions****

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, stomach pain,abdominal discomfort	distended abdomen, dry mouth, flatulence, mouth ulceration, vomiting	diarrhoea
Skin and subcutaneous tissue disorders	acne, hyperhidrosis, seborrhoea		alopecia, dry skin, hirsutism, cracked nails, pruritus, skin rash	angioneurotic oedema, urticaria
Musculoskeletal and connective tissue disorders		arthralgia, muscle spasms, pain in arms and legs	back pain, myalgia	muscle weakness
Reproductive system and breast disorders	changes in breast, pain on intercourse, genital bleeding (including vaginal bleeding, withdrawal bleeding), ovarian hyperstimulation syndrome, ovarian hypertrophy, pelvic pain, vaginal dryness	pain in breasts	coital bleeding, cystocele, menstruation disturbances (including dysmenorrhoea, breakthrough bleeding and heavy menstrual bleeding), ovarian cyst, vaginal discharge	amenorrhoea
General disorders and administration site conditions	asthenia	injection site reaction (including pain, swelling, erythema and inflammation), oedema peripheral, fatigue		pyrexia, malaise
Investigations		weight increase	weight loss	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 after initial administration in patients with a pituitary adenoma.
**** During post market experience convulsions have been reported in patients receiving GnRH analogues, including triptorelin

At the start of treatment, during the initial increase in oestradiol levels in plasma, it is very common ((≥ 10%) for the symptoms of endometriosis including pelvic pain, dysmenorrhea, to worsen. These symptoms are transient and usually disappear within one or two weeks. Genital bleeding including heavy menstrual bleeding and breakthrough bleeding may occur in the month following the first injection.

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

Breast Cancer
During the 5 years during which the TEXT and SOFT studies were conducted, the most commonly observed adverse reactions for triptorelin treatment in combination with tamoxifen or an aromatase inhibitor were hot flashes, musculoskeletal symptoms, fatigue, insomnia, hyperhidrosis, vaginal 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
Metabolism and nutrition 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 bleeding	
Psychiatric disorders	insomnia, reduced libido, depression			
Renal and urinary disorders	urinary incontinence			
Reproductive system and breast disorders	pain on intercourse, vaginal dryness			
Skin and subcutaneous tissue disorders	hyperhidrosis			
Vascular disorders	hot flush, hypertension	embolism		

The adverse reactions listed above must only be considered supplemental to those adverse reactions already identified in men and women in the tables above; these describe the adverse reaction profile for use of ovarian function suppression (OFS) in combination with either exemestane or tamoxifen.

A higher frequency of osteoporosis has been reported when triptorelin has been used in combination with exemestane than in combination with tamoxifen (39% versus 25%) (see section 4.4).

Musculoskeletal symptoms and fractures have also been reported more often in combination with exemestane than in combination with tamoxifen (89% versus 76% and 6.8% versus 5.2% respectively).

Hypertension, which has been studied closely, has been reported to be a "very common" adverse reaction both when triptorelin has been combined with exemestane and when it has been combined with tamoxifen (23% and 22% respectively).

Hyperglycaemia and diabetes, which have also been studied closely, have been reported with the same frequency both when triptorelin has been combined with exemestane and when it has been combined with tamoxifen (hyperglycaemia: 2.6% and 3.4%; diabetes: 2.3% and 2.3%).

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 swings	affect lability, depression, nervousness
Nervous system disorders		headache		Idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4) Convulsions*
Eye disorders			Visual impairment	visual disturbance
Vascular disorders		hot flushes		hypertension
Respiratory, thoracic and mediastinal disorders			epistaxis	
Gastrointestinal disorders		stomach pain	vomiting, constipation, nausea	
Skin and subcutaneous tissue disorders		acne	itching, skin rash, urticaria	angioneurotic oedema
Musculoskeletal and connective tissue disorders			neck pain	myalgia
Reproductive system and breast disorders	vaginal bleeding (including bleeding, withdrawal bleeding, uterine bleeding, 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

System Organ Class	Very Common AEs	Common AEs	Uncommon	Additional post-marketing AEs Frequency not known
				increased

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

Vaginal bleeding may occur in the month after the first injection.

Pressure sensitive infiltrations at the injection site have been reported as an uncommon adverse reaction for other triptorelin products after subcutaneous injection.

Reporting suspected adverse reactions.
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

gonadotropin releasing hormone analogues.

ATC code: L02AE04

Mechanism of action and pharmacodynamic effects

Triptorelin, the active substance in Decapeptyl depot, is a GnRH agonist with a similar structure 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 results in greater and more long-lasting effect from the release of LH and FSH from the pituitary gland than natural GnRH.

Initially, triptorelin causes a transient increase in LH and FSH release, with accompanying elevated testosterone, oestrogen and progesterone levels in plasma. The gonadotropin release is then suppressed, which leads to testosterone or oestrogen in the plasma falling to castration prepubertal or postmenopausal values after 2-4 weeks.

Subsequent injections of Decapeptyl depot do not cause 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
Following an intramuscular injection of Decapeptyl depot 3.75 mg in healthy male volunteers, the serum testosterone levels did not increase to the maximum level until day 4 before then falling to low levels by 4 weeks. After week 8, the levels had increased once more. A similar change in testosterone

levels was observed in patients with advanced prostate cancer who received intramuscular injections of triptorelin embonate. After the second injection, the testosterone levels remained within the castration limit.

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 randomized 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 randomized to receive E+OFS, T+OFS or T alone. In the TEXT study women were included following breast surgery and randomized 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).

<u>SOFT study results</u>

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

Decapeptyl depot contains triptorelin in the form of bioabsorbablemicro particles that are suspended in a water phase, injected intramuscularly and and constitute a prolonged-release preparation with the gradual release of the active ingredient. Maximum plasma concentration is achieved within one hour after administration and falls rapidly to steady state. Therapeutic plasma concentrations well above the level required to sustain the pharmacodynamic effect are maintained throughout 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 fairly high global interindividual variation, oestradiol suppression for approx. 30 days was seen 5 days after intramuscular injection of Decapeptyl depot 3.75mg.

5.3 Preclinical safety data

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

Triptorelin is not mutagenic in vitro or in vivo. No oncogenic effect has been demonstrated with triptorelin in mice at doses up to 6,000 µg/kg after 18 months of treatment. A 23-month

carcinogenicity study in rats has shown an almost 100% occurrence of benign pituitary gland tumours (pituitary adenomas) at every dose level, which leads to premature death. The increased occurrence of pituitary gland tumours in rats is a common effect associated with GnRH agonist treatment. The clinical relevance of this is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 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 powder must be reconstituted aseptically and only using the ampoule of dilution liquid provided. The instructions for dilution below and which are provided in the package leaflet must be followed exactly. Draw up the dilution liquid into the syringe provided by using the reconstitution needle and then transferring the liquid to the injection vial containing the powder Reconstitute the powder by carefully shaking the injection vial from side to side in an oscillating movement until a homogeneous, milk-like suspension forms. Do not turn the injection vial upside down. It is important to check there is no unsuspended powder in the vial.

Draw the suspension that has formed back into the syringe, without turning the injection vial upside down. Then replace the needle with the injection needle that does have a prick guard (20 G) and will be used for administration later on. Since the product is a suspension, it must be injected immediately after reconstitution to avoid deposits forming.

Intended 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 OF THE PATIENT BEFORE RECONSTITUTION

Prepare the patient by disinfecting his/her gluteus at the injection site. This operation needs to be performed first because once reconstituted, the drug should be injected immediately.

Preparation for injection.

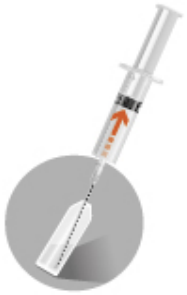
Two needles are provided in the box:

- The reconstitution needle
- The injection needle
- The presence of bubbles on top of the lyophilisate is a normal appearance of the product.

The following steps must be completed in a continuous sequence.

2a

- Take out the ampoule containing the solvent. Tap any solution within the tip of the ampoule back to the main body of the ampoule.
- Screw the reconstitution needle onto the syringe (do not remove the needle cover at this point!)
- Break open the solvent ampoule with dot face up.
- Remove the needle cover from the reconstitution needle. Insert the needle in the ampoule and draw up all the solvent into the syringe.



Put aside the syringe containing the solvent.

2b

- 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.

o Take back the syringe containing the solvent again and insert the needle thorogh the rubber stopper vertically into the vial

o Inject the solvent slowly so that it if possible, it washes down the entire upper part of the vial.

2.c

- Pull up the needle to above the liquid level
- Do not remove the needle from the vial. Reconstitute the suspension by swirling gently from side to side. Do not invert the vial.

- Make sure that the agitation is long enough (at least 30 seconds) to obtain an homogeneous and milky suspension.

- **Important: Check there is no unsuspended powder in the vial (if any powder clumps are present, continue swirling until they disappear)**

2d

- When the suspension is homogeneous, pull down the needle without inverting the vial, draw up all of the suspension. A small amount will remain in the vial and should be discarded. An overfill is included to allow for this loss.

- Remove the needle used for the reconstitution from the syringe. Screw on to the syringe needle for injections.
- Prime the needle to remove air from the syringe and inject immediately.

Intramascular Injection

- To avoid sedimentation, inject immediately into the disinfected area as quickly as possible (within 1 minute from reconstitution).

After use

- Dispose of the needles 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 3088900, Israel.

9. Registration number: 132-28-28860

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