Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Leuprex 3, 5mg Implant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each implant contains 5 mg of leuprorelin (as leuprorelin acetate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Implant.

White to slightly yellowish cylinder-shaped stick (length 10 mm) in a pre-filled syringe.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Palliative treatment of patients with advanced hormone-dependent prostate carcinoma.
- Treatment of locally advanced, hormone-dependent prostate cancer; concomitantly and after radiotherapy
- Treatment of localised, hormone-dependent prostate cancer in patients with intermediate and high risk in combination with radiotherapy.

4.2 Posology and method of administration

Posology
The indication for treatment should be established and the long-term therapy monitoring carried out by physicians experienced in tumour therapy.

The recommended dose is a single-dose of 5 mg leuprorelin once every 3 months.
If, in exceptional cases, the date of administration is postponed by up to 4 weeks, the therapeutic effect should not be impaired in the majority of patients (see section 5.2).

Special populations
No dosage adjustment is necessary for patients with renal or hepatic impairment, or in older people.

Paediatric population
Leuprex 3, 5 mg Implant is contraindicated in children and adolescents, see section 4.3.

Leuprex 3, 5 mg Implant can be used as neoadjuvant or adjuvant therapy in combination with radiotherapy in locally advanced, hormone sensitive prostate cancer as well as in localised prostate cancer in patients with moderate and high risk profile.

Method of administration
Leuprex 3, 5 mg Implant should be prepared and administered only by healthcare professionals who are familiar with these procedures.
One implant is injected subcutaneously into the anterior abdominal wall.

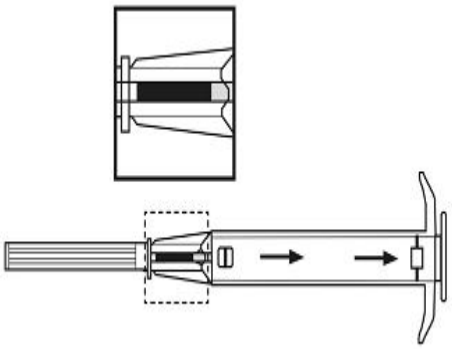
Before injection, a local anaesthetic may be given.

It is recommended that administration of an anti-androgen is started as adjunctive therapy about 5 days before starting Leuprex 3, 5 mg Implant (see section 4.4).

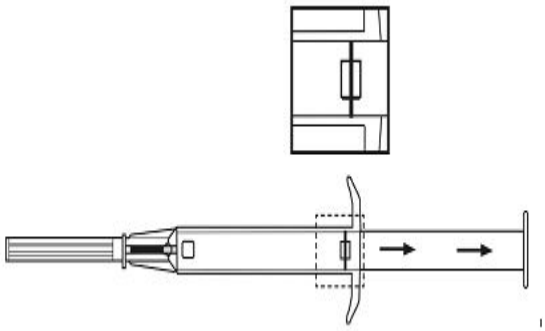
Instructions for use:

Read these instructions carefully, as the applicator provided with this medicine could be different to others you have used.

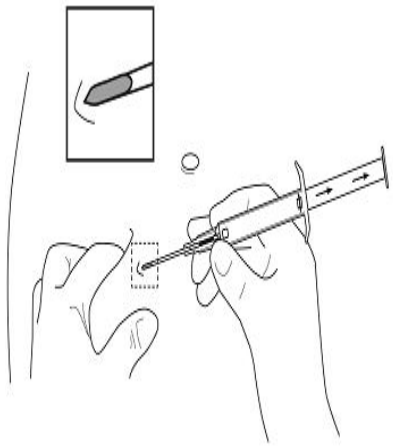
1. Disinfect the injection site on the anterior abdominal wall below the navel line.
2. Remove the applicator from the sterile bag and check that the implant is visible in the repository (see framed area). For verifying, view the applicator against a light or gently shake it.



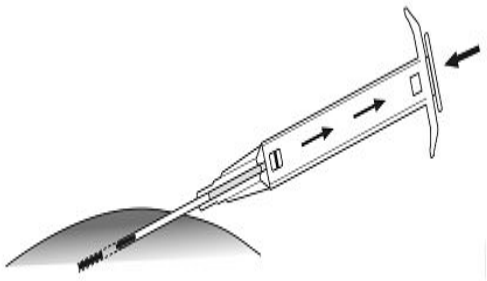
3. Pull the plunger of the applicator **completely backwards until you can see a complete line in the second window.**
Please note: The plunger can only be pushed forward to inject the implant if it has been previously pulled back completely!



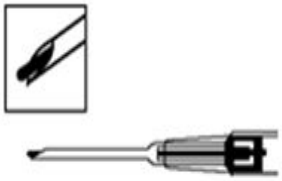
4. Remove the protective cap from the needle.
5. Hold the main body of the applicator with one hand. With the other hand pinch the patient's skin of the anterior abdominal wall below the navel line. See illustration. With the **needle opening facing upwards,** insert the whole needle. Do this at a slight angle, almost parallel to the skin into the subcutaneous tissue



6. Carefully pull the applicator approximately **1cm backwards.** This creates the puncture canal for the implant.
7. Inject the implant into the puncture canal by pushing the plunger **completely** forwards until it snaps into place and you **hear a click**.



8. Withdraw the needle. To ensure that the implant has been injected correctly, check that the light blue tip of the plunger is visible at the tip of the needle.



Both PSA and total testosterone levels in serum must be determined at the beginning and after 3-month use of Leuprex 3, 5 mg Implant. The prostatic carcinoma is androgen-sensitive when testosterone concentrations are at castrate level (≤ 0.5 ng/ml) after 3 months and the PSA value has decreased. An early marked decline in the PSA value (approx. 80% of the baseline value) can be seen as a good prognostic indicator for long-term response to androgen withdrawal. Hormone-ablative therapy (e.g. Leuprex 3, 5 mg Implant is then indicated.

When PSA values remain unchanged or have increased in patients with suppressed testosterone the prostatic carcinoma is androgen-insensitive. In such cases, continuation of hormone-ablative therapy is not suitable.

However, if the patient has shown a clinical response (e.g. improvement in pain and dysuria symptoms, reduction in size of prostate), the result must be considered to be a false negative. In these rare cases, administration of Leuprex 3, 5 mg Implant should be continued for another 3 months and the PSA value be checked again; moreover, the patient should be very closely monitored with regard to clinical symptoms.

Therapy of advanced, hormone-dependent prostate carcinoma with Leuprex 3, 5 mg Implant is generally a long-term therapy.

It has been shown in clinical trials that in locally advanced, hormone sensitive prostate in combination with radiotherapy an androgen-deprivation therapy duration of 3 years is to be preferred over a duration of 6 months (please refer to section 5.1). Clinical guidelines recommend a duration of androgen-deprivation therapy of 2-3 years in patients (T3-T4) receiving radiotherapy.

In localised prostate cancer in patients with moderate risk profile the combination of radiotherapy with androgen-deprivation therapy with LHRH agonists is recommended for 4 to 6 months, whereas in patients with high-risk profile it is recommended for 2 to 3 years.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to other LHRH analogues.

Confirmed hormone independence of the carcinoma **Leuprex 3 is contraindicated in women and paediatric patients.**

4.4 Special warnings and precautions for use

Patients with hypertension should be carefully monitored.

There is an increased risk of depression (which may be severe) in patients being treated with LHRH agonists (gonadotropin-releasing hormone agonists) such as leuprorelin. Patients must be informed of this risk and be treated as appropriate if symptoms occur.

Allergic and anaphylactic reactions have been observed. They include both local reactions at the site of injection and systemic symptoms.

Post marketing reports of convulsions have been observed in patients on leuprorelin acetate therapy with or without a history of epilepsy, convulsions or predisposing factors.

Following surgical castration leuprorelin causes no further reduction of testosterone concentration.

On account of the short-term increase in the serum testosterone concentration at the start of treatment, which can temporarily intensify certain symptoms of disease, patients with a risk of neurological complications, spinal metastasis and urinary tract obstruction should be constantly monitored during the first weeks of treatment, as far as possible as in-patients.

The additional administration of a suitable anti-androgen should be considered for the initial phase of treatment, to mitigate the possible sequela of the initial testosterone surge and the worsening of the clinical symptoms.

Therapeutic success should be regularly monitored (but particularly if there is evidence of progression despite appropriate treatment) by means of clinical examinations (digital rectal examination of the prostate, ultrasound, skeletal scintigraphy, computed tomography) and by checking phosphatases and/or the prostate specific antigen (PSA) and serum testosterone concentration.

Hypogonadism occurring with long-term treatment with LHRH analogues and/or orchiectomy can lead to osteoporosis with an increased risk of fracture, the development of osteoporosis being more marked following orchiectomy, with increased cortisol levels, than following administration of LHRH analogues. In high-risk patients the additional administration of a bisphosphonate may prevent bone demineralisation.

A change in glucose tolerance has been reported in some patients being treated with LHRH analogues. Diabetics must be very closely monitored during treatment with Leuprex 3.

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Leuprex 3, 5mg Implant.

Idiopathic intracranial hypertension
Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving leuprorelin. 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 leuprorelin should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Leuprex 3 with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Leuprex 3 is intended only for use in male patients.

4.7 Effects on ability to drive and use machines

This medicinal product may alter reactivity to such an extent, even when used as intended, that the ability to drive and use machines is impaired. This is due to the fatigue occurring in a few patients, particularly at the start of treatment, which may also be caused by the underlying tumour disease.

This applies to an even greater extent in combination with alcohol.

4.8 Undesirable effects

Initially there is normally a short-term increase in the serum testosterone concentration, which can temporarily aggravate certain symptoms of disease (bone pain or an increase in bone pain, obstruction of the urinary tract and its consequences, spinal cord compression, muscle weakness in the legs, lymphatic oedema). This increase in symptoms normally regresses spontaneously without Leuprex 3 having to be discontinued.

Undesirable effects may occur due to the withdrawal of the sex hormones

Tabulated list of adverse reactions:

The side effects are listed based on system organ class and MedDRA frequency convention:
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
Very rare: < 1/10,000
Not known: frequency cannot be estimated from the available data

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders			general allergic reactions (fever, itching, eosinophilia, skin rash)	anaphylactic reactions		
Metabolism and nutrition disorders		decreased appetite, increase in appetite,		changes in diabetic metabolic status (increase or decrease in blood glucose levels)		
Psychiatric disorders		Mood changes, depression, sleep disorders				
Nervous system disorders		headache, paraesthesia		vertigo, transient dysgeusia	As with other medicinal products in this substance class, there have been reports of very rare cases of pituitary apoplexy following initial administration of leuprorelin in patients with pituitary adenoma.	Convulsion, Idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)

Cardiac disorders						QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	hot flushes			changes in blood pressure (hypertension or hypotension), thrombosis		
Respiratory, thoracic and mediastinal disorders				pulmonary embolism		Interstitial lung disease
Gastrointestinal disorders		nausea/vomiting	diarrhoea			
Skin and subcutaneous tissue disorders			dry skin or mucosa, nocturnal sweating	alopecia		
Musculoskeletal and connective tissue disorders	Bone pain	Joint and/or back pain, myasthenia,				Bone demineralisation (see section 4.4)
Renal and urinary disorders		nocturia, dysuria, pollakiuria	urinary retention			
Reproductive system and breast disorders	reduction in - or loss of - libido and sexual potency, reduction in size of the testicles	gynaecomastia	testicular pain			
General disorders and administration site conditions	increased sweating; reactions at the injection site, e.g. reddening, pain, oedema, itching which usually subsided even when treatment was continued.	fatigue, peripheral oedema,				
Investigations	weight gain	Weight loss, increases in LDH, transaminases (ALT, AST), gamma-GT and alkaline phosphatase,				

		which may also be a manifestation of the underlying disease.				

There have been post-marketing reports of interstitial pneumonia mainly in Japan.

Special notes
The response to **Leuprex 3** therapy can be monitored by measuring serum concentrations of testosterone, acid phosphatase and PSA (prostate-specific antigen). Testosterone levels initially increase upon initiation of therapy, but decreases over a period of 2 weeks. After 2 - 4 weeks, the testosterone concentrations reached are comparable to those observed following bilateral orchiectomy, remaining then constant over the entire treatment period.

A transient increase in acid phosphatase levels may occur in the initial phase of treatment. Normal levels or levels approaching normal are usually reached again after a few weeks.

In rare cases injection abscesses have occurred. In one case of injection abscesses inadequate absorption of leuprorelin from the depot formulation was observed, therefore testosterone levels should be monitored in such cases.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No symptoms of intoxication have been observed to date.

Even when doses were administered of up to 20 mg leuprorelin acetate per day for 2 years, as was the case in the first clinical studies, no other or new undesirable effects were observed which differed from those occurring after daily administration of 1 mg or three-monthly administration of 11.25 mg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormones and related agents, Gonadotropin releasing hormone analogues
ATC code: L02AE02

Leuprorelin acetate, the active substance of Leuprex 3, 5 mg Implant, is a synthetic analogue of the naturally-occurring hypothalamic "releasing factor" LHRH, which controls the release of the gonadotropic hormones LH (luteinising hormone) and FSH (follicle-stimulating hormone) from the anterior lobe of the pituitary gland These hormones in turn stimulate the synthesis of gonadal steroids.

Unlike physiological LHRH, which is released in a pulsatile manner from the hypothalamus, leuprorelin acetate - also known as LHRH agonist - blocks the LHRH receptors of the pituitary gland continuously during long-term therapy, and after initial short-term stimulation causes their down regulation. As a result, there is reversible pituitary suppression of gonadotropin release with a subsequent decrease in testosterone concentrations.

The testosterone concentration is lowered and this consequently influences growth carcinomatous prostate tissue, which is normally stimulated by dihydrotestosterone, produced by the reduction of testosterone in prostatic cells.

Continuous administration of leuprorelin acetate leads to a decrease in the number and/or sensitivity (so-called "down regulation") of receptors in the pituitary gland, and consequently to a decrease in the concentrations of LH, FSH and DHT., In the process the testosterone level is reduced to the castration level.
An anti-androgenic effect and growth inhibition of prostatic carcinomas have also been demonstrated in animal trials.

According to preclinical and clinical studies, monthly treatment with leuprorelin acetate inhibits the release of gonadotropin after initial stimulation.

In man, subcutaneous administration of leuprorelin acetate causes an initial increase in LH (luteinising hormone) and FSH (follicle-stimulating hormone), characterised by a transient increase in concentrations of testosterone and dihydrotestosterone.

Since an associated short-term symptomatic aggravation of the disease has been observed in the first 3 weeks in isolated cases, adjuvant administration of anti-androgens is to be considered in men with prostate carcinoma.

In contrast, long-term therapy with leuprorelin acetate causes a decrease in LH and FSH concentrations in all patients; androgen concentrations in men are reached similar to those following bilateral orchiectomy. These changes usually appear 2 - 3 weeks after start of therapy and are maintained for the entire treatment period. For that reason, the hormonal sensitivity of prostatic carcinomas and the possible therapeutic value of orchiectomy can also be investigated with leuprorelin acetate. If necessary, orchiectomy may be replaced by monthly administration of leuprorelin acetate. So far, it has been possible to maintain castrate testosterone levels following continuous administration of leuprorelin acetate over 5 years.

Clinical efficacy
In a multicentre, randomized Phase III study with leuprorelin acetate 263 patients with locally advanced prostate carcinoma of the stages T3-T4 or pT3, N0, M0 were evaluated. 133 patients received a combination of radiotherapy with androgen deprivation therapy and 130 patients androgen deprivation therapy with leuprorelin acetate alone over 3 years.
Based on the ASTRO (Phoenix criteria, the progression-free survival over 5 years was 60.9% (64.7%) in the combination therapy compared to 8,5 % (15,4 %) in the group with hormone therapy alone ($p = 0,0001$; [$p = 0,0005$]).
According to ASTRO-criteria, the risk of progression was 3.8-times higher in the group with hormone therapy alone (95 % CI [2,17; 6,49]).
The median clinical or biochemical progression-free survival according to ASTRO criteria was 641 days (95 % CI [626; 812]) in the group with hormone therapy alone versus 2.804 days (95 % CI [2.090; –]; $p < 0,0001$) in the group with combination therapy.
There were no statistically significant differences regarding locoregional progression (HR 3,6 [95 % CI {1,9; 6,8}; $p < 0,0001$]), metastatic progression ($p < 0,018$) and metastases-free survival ($p = 0,018$) in the combination therapy group versus androgen deprivation therapy alone.
It could be clearly shown in this trial that the combination of androgen deprivation therapy with radiotherapy over 3 years is superior in comparison to androgen deprivation therapy alone.

The following trials shows that the combination therapy with LHRH analogues is also superior to radiotherapy alone in patients with locally advanced prostate cancer. In the randomised RTOG 85-31 trial 977 patients with locally advanced prostate carcinoma stage T1-T3 with metastases in the lymph nodes, breakthrough of the prostate or penetration of prostate cancer in the seminal vesicles have been included. 488 patients received a combination of radiotherapy with long-term androgen deprivation therapy with gosereline whereas 489 patients received radiotherapy alone. The results clearly show that the combination therapy is superior versus radiotherapy alone. 10- year progression-free survival was 37% versus 23% ($p < 0,001$); progression-free survival with a PSA-value < 1,5 ng/ml was 31 % versus 9 %, local recurrence occurred in 23 % versus 38 % ($p < 0,0001$) and progression with metastases occurred in 24 % versus 39 %($p < 0,0001$). Overall survival was 49 % versus 39 % ($p = 0,002$) and disease-specific mortality was 16 % versus 22 % ($p = 0,0052$).

The superiority of the combination of radiotherapy with androgen deprivation therapy with LHRH analogues in comparison to radiotherapy alone in patients with localised prostate cancer with moderate risk profile has been shown in the following clinical trial.

The randomised phase III clinical trial RTOG 94-08 has been conducted in patients with localised prostate cancer stage T1b, T1c, T2a or T2b and a PSA-value ≤ 10 ng/ml. The patient subgroup with a moderate risk profile defined by a Gleason-Score 6 in combination with a PSA-value ranging from > 10 ng/ml to 20 ng/ml or stage T2b included 524 patients in the short time androgen deprivation therapy group over 4 months (2 months before and 2 months in combination with radiotherapy) and 544 patients in the group with radiotherapy alone. In the subgroup with moderate risk profile, the group which received a

combination of radiotherapy and androgen deprivation therapy with goserelin or leuprorelin acetate was superior to the group which received radiotherapy alone.

Overall survival after 10 years was 61 % versus 54 % (hazard ratio 1,23, 95 % CI [1,02-1,49; p = 0,03]). Disease-specific mortality was 3 % versus 10 % (hazard ratio 2,49, 95 % CI [1,50-4,11; p = 0,004]) and biochemical progression was 28 % versus 45 % (hazard ratio 1,79, 95 % CI [1,45-2,21; p < 0,001]).

The use in patients with localised prostate cancer with high risk profile is based on published clinical trials for radiotherapy in combination with LHRH agonists including leuprorelin acetate.
Clinical data has been published in five clinical trials which all clearly show the advantage of the combination of radiotherapy with LHRH-agonists ((EORTC 22863, RTOG 85-31, RTOG 92-02, RTOG 8610 und D'Amico et al.,JAMA 2004). A clear differentiation of the study population between the indications locally advanced prostate cancer and localised prostate carcinoma with high risk profile was not possible.
It has been shown in clinical data that radiotherapy followed by 3 years androgen deprivation therapy should be preferred versus radiotherapy followed by 6 months androgen deprivation therapy.

The duration of androgen deprivation therapy of 2-3 years in patients with stage T3 to T4 is recommended in clinical guidelines.

In patients with metastatic castration-resistant prostate cancer the benefit of additional agents like androgen synthesis inhibitors (e.g. abiraterone acetate), antiandrogens (e.g. enzalutamide), taxanes (e.g. docetaxel or paclitaxel) or agents for radiotherapy (e.g. Radium-223) in addition to LHRH agonists like leuprorelin acetate has been shown.

5.2 Pharmacokinetic properties

The active substance, leuprorelin acetate, is continuously released from the lactic acid polymer over a period of up to 182 days (26 weeks) following injection of the Leuprex 3biodegradable implant. The polymer is absorbed in the same way as surgical suture material.

Within 2 hours after subcutaneous single-dose application of Leuprex 3, peak serum leuprorelin levels of 5216 pg/ml (5.2 ng/ml) have been measured.

The AUC during 3 months' treatment with Leuprex 3 was 32.4 ng/ml*d.
Detectable levels in serum are present for up to 182 days (26 weeks) after administration.

The volume of distribution for leuprorelin is 36 l in men; total clearance is 139.6 ml/min.

In patients with impaired renal or hepatic function, leuprorelin levels were in the range of those seen in patients with healthy kidneys or livers. In some patients with chronic renal failure, higher leuprorelin serum levels were measured. However, this observation does not seem to be of any clinical relevance.

5.3 Preclinical safety data

Preclinical studies on leuprorelin acetate have shown effects on the reproductive organs, which were expected on the basis of known pharmacological properties of leuprorelin.

Carcinogenicity
In rats, a dose-dependent increase in pituitary adenomas was observed following subcutaneous injection of doses of 0.6 - 4 mg/kg/day over 12 and 24 months. No such effect was observed in mice over 24 months.

Mutagenicity
In vitro and *in vivo* studies on leuprorelin acetate for the detection of genetic and chromosome mutations yielded no evidence of any mutagenic potential.

Toxicity to reproduction
In reproductive toxicity studies on rabbits, increased foetal mortality and reduced foetal weight were observed. Effects on foetal mortality are anticipated consequences of the pharmacodynamic effect of this substance.

Local tolerance
Non-clinical studies on dogs and rabbits revealed a good local tolerance of Leuprex 3.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polylactic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Pre-filled plastic syringe of polycarbonate with a plunger of acrylonitril-butadien-styrene copolymer and a needle sealed in a bag of polyethylene terephthalate/aluminium/PE composite foil.

Pack sizes:
1 x 1 implant with 5 mg leuprorelin (as acetate)
2 x 1 implant with 5 mg leuprorelin (as acetate)
3 x 1 implant with 5 mg leuprorelin (as acetate)
5 x 1 implant with 5 mg leuprorelin (as acetate)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/188/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 2009
Date of last renewal: 19th April 2012

10 DATE OF REVISION OF THE TEXT