Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

PROSTAP 3 DCS 11.25 mg Powder and Solvent for Prolonged-release Suspension for Injection in Pre-filled Syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder: Each single-dose syringe contains 11.25mg leuprorelin acetate.

When reconstituted with Sterile Solvent, the suspension contains 11.25 mg leuprorelin acetate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged–release suspension for injection in pre-filled syringe (Dual Chamber Syringe)

Powder: A sterile, lyophilised, white, odourless powder.
Solvent: A colourless, odourless, slightly viscous, aqueous sterile solvent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

(i) Management of prostatic carcinoma for which a suppression of testosterone is indicated.

(ii) Management of estrogen dependent gynaecological disorders including the management of pain and lesions associated with endometriosis.

(iii) Preoperative management of uterine fibroids to reduce their size and associated bleeding.

(iv) As treatment in pre- and perimenopausal women with advanced breast cancer suitable for hormonal manipulation.

(v) As adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in pre- and perimenopausal women at higher risk of disease recurrence (young age, high grade tumour, lymph node involvement). In women who have received chemotherapy, premenopausal status must be confirmed after completion of chemotherapy.

In children:
Treatment of central precocious puberty (girls under 9 years of age, boys under 10 years of age).

4.2 Posology and method of administration

Posology

Male Adults: The recommended dose is 11.25mg presented as a 3 month depot injection and administered as a single subcutaneous or intramuscular injection at intervals of 3 months. The majority of patients will respond to this dosage. PROSTAP 3 therapy should not be discontinued when remission or improvement occurs.

Response to PROSTAP 3 therapy should be monitored by clinical parameters and by measuring prostate-specific antigen (PSA) and testosterone serum levels. Clinical studies have shown that testosterone levels increased during the first 4 days of treatment in the majority of non-orchidectomised patients. They then decreased and reached castrate levels in 2-4 weeks. Once attained, castrate levels were maintained as long as drug therapy continued. Transient increases in PSA levels sometimes occur early in the treatment period but usually return to normal or near normal values by the 4th week of treatment.

In patients treated with GnRH analogues for prostate cancer, treatment is usually continued upon development of castrate-resistant prostate cancer. Reference should be made to relevant guidelines.

Female Adults:
Treatment options for vasomotor symptoms and bone mineral density loss should be considered.

Endometriosis
The recommended dose is 11.25mg administered as a single subcutaneous or intramuscular injection every 3 months for a period of up to 6 months. Treatment should be initiated during the first 5 days of the menstrual cycle.

Preoperative management of uterine fibroids
The recommended dose is 11.25mg administered as a single subcutaneous or intramuscular injection every 3 months for a maximum of 6 months.

Advanced breast cancer:
The recommended dose is 11.25 mg administered as a single subcutaneous injection every 3 months.

Early breast cancer:
The recommended dose is 11.25 mg administered as a single subcutaneous injection every 3 months in combination with tamoxifen or an aromatase inhibitor.

In women receiving chemotherapy, leuprorelin should be commenced after completion of chemotherapy, once pre-menopausal status has been confirmed (see section 4.4).

The recommended treatment duration for adjuvant treatment in combination with other hormonotherapy is up to 5 years.

In combination with aromatase inhibitor for advanced and early breast cancer:
Treatment with leuprorelin must be initiated at least 6-8 weeks before starting aromatase inhibitor treatment. A minimum of one injection of PROSTAP 3 should be administered before commencement of aromatase inhibitor treatment.

Ovarian suppression should be confirmed by low blood concentrations of FSH and estradiol prior to starting aromatase inhibitor treatment and measurements should be repeated every three months during combination therapy with leuprorelin and an aromatase inhibitor (see Section 4.4).

During treatment with an aromatase inhibitor, leuprorelin must not be interrupted to avoid rebound increases in circulating estrogens in premenopausal women.

Elderly: As for adults.

Paediatric population:

The treatment of children with leuprorelin acetate should be under the overall supervision of the paediatric endocrinologist.

The dosing scheme needs to be adapted individually.

The recommended starting dose is dependent on the body weight.

Children with a body weight ≥ 20 kg
1 ml (11.25 mg leuprorelin acetate) suspension of 130.0 mg sustained-release microcapsules in 1 ml vehicle solution are administered every 3 months as a single subcutaneous injection.

Children with a body weight < 20 kg
In these rare cases the following dosage should be administered according to the clinical activity of the central precocious puberty:
0.5 ml (5.625 mg leuprorelin acetate) suspension of 130.0 mg sustained-release microcapsules in 1 ml vehicle solution are administered every 3 months as a single subcutaneous injection.
The remainder of the suspension should be discarded. The child's weight gain should be monitored.
Depending on the activity of the central precocious puberty, it may be necessary to increase the dosage in the presence of inadequate suppression (clinical evidence e.g. spotting or inadequate gonadotropin suppression in the GnRH test). The minimal effective 3-monthly dose to be administered should then be determined by means of the GnRH test.

Sterile abscesses at the injection site often occurred when leuprorelin acetate was administered intramuscularly at higher than the recommended dosages. Therefore, in such cases, the medicinal product should be administered subcutaneously (see 4.4).
It is recommended to use the lowest volumes possible for injections in children in order to decrease the inconvenience which is associated with the intramuscular/subcutaneous injection.
The duration of treatment depends on the clinical parameters at the start of treatment or during the course of treatment (final height prognosis, growth velocity, bone age and/or bone age acceleration) and is decided by the treating paediatrician together with the legal guardian and, if appropriate, the treated child. The bone age should be monitored during treatment at 6-12 month intervals.

In girls with bone maturation of older than 12 years and boys with bone maturation of older than 13 years discontinuation of treatment should be considered taking into account the clinical parameters.
In girls, pregnancy should be excluded before the start of treatment. The occurrence of pregnancy during treatment cannot be generally excluded. In such cases, medical advice should be sought.
Note:
The administration interval should be 90 ± 2 days in order to prevent the recurrence of precocious puberty symptoms.

Method of Administration
Read this Instructions For Use before injecting.

This product should be prepared, reconstituted and administered only by healthcare professionals who are familiar with these procedures.

Warnings
Wash hands before opening the syringe package.
Hold syringe upright (with needle side up) throughout entire preparation to prevent leakage.
Use immediately after mixing as the suspension settles out very quickly following reconstitution.
Check the expiration date printed on the syringe label, and check the powder and diluent in the syringe barrel. The powder should be white and dry, and the diluent should be clear. Inspect the syringe for any damage.

- **Do not** use the syringe if the expiration date has passed.
- **Do not** use the syringe if the powder appears clumped or caked.
- **Do not** use the syringe if powder or diluent appear discoloured.
- **Do not** use the syringe if any part of it is damaged.

Step 1.Attach plunger and tighten needle

- Remove the plunger from the package.
- Screw the plunger rod into the bottom of the syringe until the end stopper begins to rotate.
    - **Do not** twist or pull the plunger rod back once it has been attached.
- Without removing the needle cap, twist the needle to the right (clockwise) to ensure it is secured tightly.
- **Do not** remove needle cap until you are ready to inject.

Step 2.Release diluent

- Holding the syringe upright, release the diluents by **slowly** pushing the plunger until the middle stopper reaches the blue line in the middle of the syringe. You should see the diluent flowing into the interior chamber above the blue line.
- **Do not** push the plunger too quickly or push past the blue line as these actions may cause leaking.
- **Do not** withdraw plunger again.

Step 3. Mix suspension

- Gently tap the syringe against the palm of your hand to mix the powder and diluent until it forms a uniform suspension. When properly mixed, the suspension should appear milky with no visible lumps.
    - Note: If particles stick to the stopper during mixing, dislodge them by gently tapping the syringe with your finger.

- Avoid hard tapping or shaking to prevent the generation of bubbles.
- Use immediately after mixing as the suspension settles out very quickly following reconstitution.

Step 4. Remove needle cap and prime syringe

- Remove the needle cap by pulling it straight upwards.
- **Do not** twist the needle cap.
- Prime the syringe by pushing the plunger upward until all air has been expelled from the syringe.

Step 5. Inject

- The syringe is now ready for injection. Use immediately as the suspension settles out very quickly following reconstitution.
- At the time of injection, check the direction of the safety device (with round mark pointing towards you) and inject the entire contents of the syringe subcutaneously or intramuscularly as you would for a normal injection**.**

Step 6. Activate safety device

- When injection is complete, withdraw the needle from the patient. Immediately activate the safety device by pressing upward from just below the arrow until a "CLICK" is heard or felt and the needle is fully covered.

Step 7. Dispose of syringe

- Dispose of the used device in the appropriate sharps container in accordance with your local standard procedure.

4.3 Contraindications

Hypersensitivity to leuprorelin, any of the excipients (listed in section 6.1) or to other synthetic gonadotrophin releasing hormone (Gn-RH) analogues or Gn-RH derivatives.

Men: Use in patients insensitive to endocrine therapy or in those patients post-orchidectomy.

Women: PROSTAP 3 is contra-indicated in women who are or may become pregnant while receiving the drug. PROSTAP 3 should not be used in women who are breastfeeding or who have undiagnosed abnormal vaginal bleeding. See section 4.4

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

In girls with central precocious puberty:
- Pregnancy and breastfeeding
- Undiagnosed vaginal bleeding.

4.4 Special warnings and precautions for use

PROSTAP 3 injectable suspension must be prepared at the time of use and, after reconstitution, used immediately.

Depression: There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as leuprorelin. Patients should be informed and monitored accordingly and treated as appropriate if symptoms occur.

Seizures: Postmarketing reports of seizures have been observed in patients treated with leuprorelin acetate and these events have been reported in both children and adults, and in those with or without a history of epilepsy, seizure disorders or risk disorders for seizures.

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.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN) which can be life-threatening or fatal, have been reported in association with leuprorelin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If signs and symptoms suggestive of these reactions appear, leuprorelin should be withdrawn immediately and an alternative treatment considered (as appropriate).

Metabolic changes associated with GnRH agonist may also include fatty liver disease.

Adults:
Epidemiological data have shown that androgen deprivation therapy in males and estrogen deprivation therapy in females, is associated with metabolic changes (e.g. reduction in glucose tolerance or aggravation of pre-existing diabetes) as well as an increased risk for cardiovascular diseases. However, prospective data did not confirm a link between treatment with GnRH analogues and an increase in cardiovascular mortality.Patients at high risk for metabolic changes or syndrome, or cardiovascular diseases should be appropriately monitored. Diabetic patients may require more frequent monitoring of blood glucose during treatment with PROSTAP 3.

Hepatic dysfunction and jaundice with elevated liver enzyme levels have been reported. Therefore, close observation should be made and appropriate measures taken if necessary.

Spinal fracture, paralysis and hypotension have been reported.

Bone mineral loss: Long-term estrogen deprivation either by bilateral oophorectomy, ovarian ablation or administration of GnRH analogues, or long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone mineral loss which, in patients with additional risk factors, may lead to osteoporosis and an increased risk of bone fracture (see section 4.8).

The induced hypo-estrogenic state results in a clinically significant loss in bone density over the course of treatment, some of which may not be reversible. The extent of bone demineralisation due to hypo-estrogenaemia is proportional to time. The level of bone loss seen with GnRH analogues such as PROSTAP 3 is of the order of 5%. In clinical studies the levels varied between 2.3% and 15.7% depending on the method of measurement.
In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, PROSTAP 3 therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with PROSTAP 3 is instituted. This is particularly important in women with uterine fibroids where age related bone loss may have already begun to occur.

Treatment options for vasomotor symptoms and bone mineral density loss should be considered

Men:
PROSTAP 3 should only be used under direction of a clinician having available appropriate facilities for monitoring the response to treatment.

Testosterone levels should fall to castrate values within 6 weeks. Failure to do so requires reassessment of patient selection or compliance.

In the initial stages of therapy, a transient rise in levels of testosterone, dihydro-testosterone and acid phosphatase may occur. In some cases, this may be associated with a "flare" or exacerbation of the tumour growth resulting in temporary deterioration of the patient's condition. This may lead to neurological or systemic effects. These symptoms usually subside on continuation of therapy.

In order to reduce the risk of "flare", an anti-androgen may be administered beginning 3 days prior to leuprorelin acetate therapy and continuing for the first 2 to 3 weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone.

In the rare event of an abscess occurring at the injection site, testosterone level should be monitored as there may be inadequate absorption of leuprorelin from the depot formulation.

Patients at risk of or with ureteric obstruction or spinal cord compression due to metastasis should be considered carefully and closely supervised in the first few weeks of treatment as bone pain, weakness of lower extremities and parasthesia (as neurologic symptoms) may occur. These patients should be considered for prophylactic treatment with anti-androgens. Should urological/neurological complications occur, these should be treated by appropriate specific measures.

Whilst the development of pituitary adenomas has been noted in chronic toxicity studies at high doses in some animal species, this has not been observed in long term clinical studies with PROSTAP 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 risks and benefits including the potential for Torsade de pointes prior to initiating treatment with PROSTAP 3.

Women**:**
Before starting treatment with leuprorelin acetate, pregnancy must be excluded (see section 4.3).
Since menstruation should stop with effective doses of PROSTAP 3, the patient should notify her physician if regular menstruation persists. Spotting/breakthrough bleeding may occur with PROSTAP 3 treatment.

During treatment with PROSTAP 3, patients should be instructed to prevent conception e.g. with the use of non-hormonal methods until return of menses.

Abnormal bleeding
Prior to administration of PROSTAP 3 undiagnosed abnormal vaginal bleeding must be investigated, diagnosis confirmed and relevant management initiated.

Initial increase in sex steroids
During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiological effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy.

Uterine fibroids diagnosis
In the case of uterine fibroids, it is mandatory to confirm the diagnosis of fibroids and exclude ovarian mass, either visually by laparoscopy or by ultrasonography or other investigative techniques as appropriate, before PROSTAP 3 therapy is instituted.

Uterine fibroids
In women receiving GnRH analogues for the treatment of uterine fibroids, the duration of administration of PROSTAP 3 should be limited to 6 months as its use is associated with an increased risk of bone mineral loss (see Bone mineral loss, section 4.4). If it is necessary to resume administration of leuprorelin acetate changes in bone parameters should be closely followed.

In women with submucous fibroids there have been reports of severe vaginal bleeding following administration of leuprorelin as a consequence of the acute degeneration of the fibroids. Patients should be warned of the possibility of abnormal bleeding or pain in case earlier surgical intervention is required.

Cervical resistance
PROSTAP 3 may cause an increase in uterine cervical resistance, which may result in difficulty in dilating the cervix for intrauterine surgical procedures.

Endometriosis
In women receiving GnRH analogues for the treatment of endometriosis, the duration of administration of leuprorelin acetate should be limited to 6 months, as its use is associated with an increased risk of bone mineral loss (see Bone mineral loss, section 4.4).

Breast cancer
Advanced and early breast cancer:

In order to ensure adequate ovarian suppression in pre- and perimenopausal women, treatment with leuprorelin should be administered for at least 6-8 weeks prior to commencement of an aromatase inhibitor, and 3 monthly leuprorelin injections should be administered on schedule and without interruption throughout aromatase inhibitor treatment.

Women who are premenopausal at breast cancer diagnosis and who become amenorrhoeic following chemotherapy may or may not have continued estrogen production from the ovaries. Irrespective of menstrual status, premenopausal status should be confirmed following chemotherapy and before commencement of leuprorelin, by blood concentrations of estradiol and FSH within the reference ranges for premenopausal women, in order to avoid unnecessary treatment with leuprorelin in the event of a chemotherapy-induced menopause.

Following commencement of leuprorelin, it is important to confirm adequate ovarian suppression (gonadotrophin analogue-induced menopause) by serial assessment of circulating FSH, and estradiol 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 estradiol prior to starting aromatase inhibitor treatment and measurements should be repeated every three months during combination therapy with leuprorelin and an aromatase inhibitor. This is to avoid aromatase inhibitor-induced rebound increase in circulating estrogen, 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.

Patients who have discontinued leuprorelin treatment should also discontinue aromatase inhibitors within 3 months of the last PROSTAP 3 administration.

Particular attention should also be paid to the prescribing information of co-administered medicinal products, such as aromatase inhibitors, tamoxifen, CDK4/6 inhibitors, for relevant safety information when administered in combination with leuprorelin.

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

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

Hypertension has been reported as a targeted adverse event at a very common frequency with GnRH agonist in combination with either exemestane or tamoxifen.

Premenopausal women with breast cancer receiving GnRH agonist in combination with either exemestane or tamoxifen should have regular monitoring of cardiovascular risk factors and blood pressure.

Hyperglycaemia and diabetes were reported as targeted adverse events at a common frequency with a GnRH agonist in combination with either exemestane or tamoxifen. Premenopausal women with breast cancer receiving a GnRH agonist 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 has been reported to occur in approximately 50% of patients treated with a GnRH agonist in combination with either tamoxifen or exemestane, 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.

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

Children with central precocious puberty: Before starting the therapy, a precise diagnosis of idiopathic and/or neurogenic central precocious puberty is necessary and, in girls, pregnancy must be excluded (see section 4.3).
The therapy is a long-term treatment, adjusted individually. PROSTAP 3 should be administered as precisely as possible in regular 3-monthly periods. An exceptional delay of the injection date for a few days (90 ± 2 days) does not influence the results of the therapy.

In the event of a sterile abscess at the injection site (mostly reported after i.m. injection of higher than the recommended dosage) the absorption of leuprorelin acetate from the depot can be decreased. In this case the hormonal parameters (testosterone, oestradiol) should be monitored at 2-week intervals (see 4.2).

The treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.

The occurrence of vaginal bleeding, spotting and discharge after the first injection may occur as a sign of hormone withdrawal in girls. Vaginal bleeding beyond the first/second month of treatment needs to be investigated.

Bone mineral density (BMD) may decrease during GnRH therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved, and peak bone mass in late adolescence does not seem to be affected by treatment.

Slipped femoral epiphysis can be seen after withdrawal of GnRH treatment. The suggested theory is that the low concentrations of estrogen during treatment with GnRH agonists weakens 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.

PROSTAP 3 contains sodium.
This medicine contains less than 1 mmol sodium (23 mg) per injection, that is to say it is essentially 'sodium free'.

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 PROSTAP 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

PROSTAP 3 is contraindicated for use during pregnancy and lactation.

Pregnancy: Safe use of leuprorelin acetate in pregnancy has not been established clinically. Studies in animals have shown reproductive toxicity (see Section 5.3). Before starting treatment with PROSTAP 3, pregnancy must be excluded. There have been reports of foetal malformation when PROSTAP 3 has been given during pregnancy. When used 3-monthly at the recommended dose, PROSTAP 3 usually inhibits ovulation and stops menstruation. Contraception is not ensured, however, by taking PROSTAP 3 and therefore, patients should use non-hormonal methods of contraception during treatment and after cessation of treatment until the return of menses.

Patients should be advised that if they miss successive doses of PROSTAP 3, breakthrough bleeding or ovulation may occur with the potential for conception. Patients should be advised to see their physician if they believe they may be pregnant.

If a patient becomes pregnant during treatment, the drug must be discontinued. No teratological effect has been demonstrated in rats and rabbits. The patient must be apprised of this evidence and the potential for an unknown risk to the foetus.

In girls with central precocious puberty: See section *4.3 Contraindications*.

4.7 Effects on ability to drive and use machines

PROSTAP 3 can influence the ability to drive and use machines due to visual disturbances and dizziness.

4.8 Undesirable effects

Side effects with PROSTAP 3 are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels.

The following tables list adverse reactions with leuprorelin based on experience from clinical trials as well as from post-marketing experience. Adverse reactions are grouped by MedDRA System Organ Classes and frequency classification. Frequencies are defined 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), very rare (< 1/10,000), not known (cannot be estimated from the available data)).

Men: In cases where a "tumour flare" occurs after PROSTAP 3 therapy, an exacerbation may occur in any symptoms or signs due to disease. Adverse events, which may occur particularly at the beginning of treatment include urinary tract obstruction (as urinary symptoms). In patients with spinal cord compression, bone pain, weakness of lower extremities and paresthesia (as neurologic symptoms) may also occur (see section 4.4). These symptoms subside on continuation of therapy.

Tabulated list of adverse reactions in Men

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders						anaemia (reported in medicinal products of this class), thrombocytopaenia, leucopenia
Immune system disorders						hypersensitivity reactions (including rash, pruritus, urticaria, wheezing, fever, chills and anaphylactic reactions)
Metabolism and nutrition disorders	weight fluctuation	decreased appetite				Metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance)
Metabolic disorders						Hepatic steatosis
Psychiatric disorders		insomnia, depression (see Section 4.4), mood changes (long-term use)**	mood changes (short term use)**			
Nervous system disorders		headache (occasionaly severe)	dizziness, parasthesiae		pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma, pituitary haemorrhage	paralysis (see Section 4.4), seizure, idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)
Eye disorders						visual impairment
Cardiac disorders						palpitations, QT prolongation (see Sections 4.4 and 4.5)
Vascular disorders	hot flush					pulmonary embolism, hypertension, hypotension (see Sections 4.4 and 4.5)
Gastrointestinal disorders		nausea	diarrhoea, vomiting			
Hepatobiliary disorders		hepatic function abnormal,				jaundice

		hepatic function test abnormal (usually transient)				
Skin and subcutaneous tissue disorders	hyperhydrosis					Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) (see section 4.4), Toxic Skin Eruption, Erythema Multiforme, Bullous dermatitis
Musculoskeletal, connective tissue and bone disorders	muscle weakness, bone pain	arthralgia	myalgia, weakness of lower extremities			spinal fracture, reduction in bone mineral density, osteoporosis (including spinal fracture, see Section 4.4)
Respiratory, thoracic and mediastinal disorders						Interstitial lung disease
Renal and urinary disorders						urinary tract obstruction
Reproductive system and breast disorders	Libido decreased, erectile dysfunction, testicular atrophy	gynaecomastia				
General disorders and administration site conditions	Fatigue, injection site reaction, e.g., induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis	oedema peripheral				pyrexia

** mood changes (long term use: frequency of 'common' and short term use: frequency of 'uncommon')

Women: Those adverse events occurring most frequently with PROSTAP 3 are associated with hypo-estrogenism. Estrogen levels return to normal after treatment is discontinued. The induced hypo-estrogenic state results in a loss in bone density over the course of treatment, some of which may not be reversible (see Special Warnings and Precautions for Use Section 4.4).

In women who have submucous fibroids there have been reports of severe bleeding following the administration of PROSTAP 3 as a consequence of the acute degeneration of the fibroids. Patients should be warned of the possibility of abnormal bleeding or pain in case earlier surgical intervention is required.

Tabulated list of adverse reactions in Women

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders						Anaemia (reported in medicinal products of this class), thrombocytopaenia, leucopenia

Immune system disorders						hypersensitivity reactions (including rash, pruritus, urticaria, wheezing, fever, chills and anaphylactic reactions)
Metabolism and nutrition disorders		weight fluctuation	decreased appetite, lipids abnormal			Metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance)
Metabolic disorders						Hepatic steatosis
Psychiatric disorders	insomnia	depression (see Section 4.4), mood changes (long-term use)**	mood changes (short term use)**			
Nervous system disorders	headache (occasionally severe)	parasthesiae, dizziness			pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma, pituitary haemorrhage	paralysis (see Section 4.4), seizure, idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)
Eye disorders			visual impairment			
Cardiac disorders			palpitations			
Vascular disorders	hot flush					pulmonary embolism, hypertension, hypotension (see Section 4.4)
Gastrointestinal disorders		nausea	diarrhoea, vomiting			
Hepatobiliary disorders			hepatic function test abnormal (usually transient)			hepatic function abnormal (including jaundice)
Skin and subcutaneous tissue disorders		hyperhidrosis	hair loss			Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) (see section 4.4), Toxic Skin Eruption, Erythema Multiforme, Bullous dermatitis
Musculoskeletal, connective tissue and bone disorders	bone pain	arthralgia, muscle weakness	myalgia			reduction in bone mineral density, osteoporosis (including spinal fracture, see Section 4.4)
Respiratory, thoracic and mediastinal disorders						Interstitial lung disease
Reproductive		breast				vulvovaginitis, libido

system and breast disorders		tenderness, breast atrophy, vulvovaginal dryness				decreased, vaginal haemorrhage
General disorders and administration site conditions		Oedema peripheral, injection site reaction e.g.injection site induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis	pyrexia, fatigue			

** mood changes (long term use: frequency of 'common' and short term use: frequency of 'uncommon')

In women with early breast cancer treated with a GnRH agonist, in combination with tamoxifen or an aromatase inhibitor, the following side effects have been seen:

*Very common**:*** Nausea, fatigue, musculoskeletal disorders, osteoporosis, hot flushes, hyperhidrosis, insomnia, depression, libido decreased, vulvovaginal dryness, dyspareunia, urinary incontinence, hypertension.
*Common**:*** Diabetes mellitus, hyperglycaemia, injection site reaction, hypersensitivity fracture, embolism.
*Uncommon**:*** myocardial ischaemia, cerebral ischaemia, central nervous system haemorrhage.

*Rare***:**QT prolongation.

In Children: In the initial phase of therapy, a short-term increase also known as a flare-up of the sex hormone level occurs, followed by a decrease to values within the pre-pubertal range. Due to this pharmacological effect, adverse events may occur particularly at the beginning of treatment.

Tabulated list of adverse reactions in Children

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders					Hypersensitivity (rash, pruritus, urticaria, wheezing, fever, chills and anaphylactic reactions)	
Metabolic disorders						Hepatic steatosis
Psychiatric disorders		depression (see Section 4.4), emotional lability				
Nervous system disorders		headache			pituitary apoplexy has been reported following initial administration in patients with	seizure, idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)

					pituitary adenoma, pituitary haemorrhage	
Gastrointestinal disorders		abdominal pain / abdominal cramps, nausea/vomiting				
Skin and subcutaneous tissue disorders		acne				Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) (see section 4.4), Toxic Skin Eruption, Erythema Multiforme, Bullous dermatitis
Musculoskeletal, connective tissue and bone disorders						myalgia
Respiratory, thoracic and mediastinal disorders						Interstitial lung disease
Reproductive system and breast disorders		vaginal haemorrhage, spotting**, vaginal discharge				
General disorders and administration site conditions		injection site reactions (e.g. induration, erythema, pain, abscess, swelling, nodules and necrosis)				

** In general, the occurrence of vaginal spotting with continued treatment (subsequent to possible withdrawal bleeding in the first month of treatment) should be assessed as a sign of potential underdosage. Pituitary suppression should then be determined by a gonadotropin releasing hormone (GnRH) stimulation test.

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 to HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

No case of overdose has been reported.

In animal studies, doses of up to 500 times the recommended human dose resulted in dyspnoea, decreased activity and local irritation at the injection site. In cases of overdose, the patients should be monitored closely and management should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophin-Releasing Hormone Analogues

ATC code: L02AE 02

PROSTAP 3 contains leuprorelin acetate, a synthetic nonapeptide analogue of naturally occurring gonadotrophin releasing hormone (GnRH), which possesses greater potency than the natural hormone. Leuprorelin acetate is a peptide and therefore unrelated to the steroids. Chronic administration results in an inhibition of gonadotrophin production and subsequent suppression of ovarian and testicular steroid secretion. This effect is reversible on discontinuation of therapy.

Administration of leuprorelin acetate results in an initial increase in circulating levels of gonadotrophins which leads to a transient increase in gonadal steroid levels in both men and women. Continued administration of leuprorelin acetate results in a decrease of gonadotrophin and sex steroid levels. In men serum testosterone levels, initially raised in response to early luteinising hormone (LH) release, fall to castrate levels in about 2-4 weeks.

Leuprorelin acetate is inactive when given orally.

Men (prostate cancer):
A randomised, open-label, comparative multi-centre study was performed to compare the efficacy and safety of the 3.75 mg and 11.25 mg depots of leuprorelin acetate. 48% of patients included had locally advanced disease (T3N0M0), and 52% of patients had metastatic disease. Mean serum testosterone level fell below the threshold for chemical castration (0.5 ng/ml) at one month of treatment, continuing to decrease thereafter andstabilising at a value below the castration threshold. The decline in serum prostate-specific antigen (PSA) mirrored that of serum testosterone in both groups.

In an open-label, prospective clinical trial involving 205 patients receiving 3.75 mg leuprorelin acetate on a monthly basis as treatment for metastatic prostate cancer, the long-termefficacy and safety of leuprorelin acetate was assessed. Testosterone levels were maintained below the castrate threshold over the 63-month follow up period. Median survival time exceeded 42.5 months for those receiving monotherapy and 30.9 months for those receiving leuprorelin acetate in combination with anti-androgens (this difference relating to baseline differences between groups).

In a meta-analysis involving primarily patients with metastatic disease, no statistically significant difference in survival was found for patients treated with luteinising hormone-releasing hormone (LHRH) analogues compared with patients treated with orchidectomy.

In another randomised, open-label, multi-centre comparative trial, leuprorelin acetate in combination with flutamide has been shown to significantly improve disease-free survival and overall survival when used as an adjuvant therapy to radiotherapy in 88 patients with high-risk localised (T1-T2 and PSA of at least 10 ng/mL or a Gleason score of at least 7), or locally advanced (T3-T4) prostate cancer. The optimum duration of adjuvant therapy has not been established. This US study used a higher dose of leuprorelin acetate (7.5 mg/month) which is therapeutically equivalent to the European licensed dose.

The use of a LHRH agonist may be considered after prostatectomy in selected patients considered at high risk of disease progression. There are no disease-free survival data or survival data with leuprorelin acetate in this setting.

Neoadjuvant leuprorelin acetate prior to radiotherapy has been shown to reduce prostate volume.

<u>In children:</u>
Reversible suppression of pituitary gonadotropin release occurs, with a subsequent decrease in oestradiol (E2) or testosterone levels to values in the pre-pubertal range.
Initial gonadal stimulation (flare-up) may cause vaginal bleeding in girls who are already post-menarchal at start of treatment. Withdrawal bleeding may occur at the start of treatment. The bleeding normally stops as treatment continues.

The following therapeutic effects can be demonstrated:
- Suppression of basal and stimulated gonadotropin levels to pre-pubertal levels;
- Suppression of prematurely increased sexual hormone levels to pre-pubertal levels and arrest of premature menstruation;
- Arrest/involution of somatic pubertal development (Tanner stages);
- Improvement/normalisation of the ratio of chronological age to bone age;
- Prevention of progressive bone age acceleration;
- Decrease of growth velocity and its normalization;
- Increase in final height.

Treatment result is the suppression of the pathologically, prematurely activated hypothalamic-pituitary-gonadal axis according to pre-pubertal age.

In a long-term clinical trial in children treated with leuprorelin at doses up to 15mg monthly for > 4 years resumption of pubertal progression were observed after cessation of treatment. Follow up of 20 female subjects to adulthood showed normal menstrual cycles in 80% and 12 pregnancies in 7 of the 20 subjects including multiple pregnancies for 4 subjects.

5.2 Pharmacokinetic properties

PROSTAP 3 is well absorbed after subcutaneous injection. It binds to the GnRH receptors and is rapidly degraded.

In male patients, an initially high plasma level of leuprorelin acetate peaks at around 3 hours after PROSTAP 3 injection, followed by a decrease to maintenance levels in 7 to 14 days. PROSTAP 3 provides continuous plasma levels for up to 117 days resulting in suppression of testosterone to below castration level within 4 weeks of the first injection in the majority of patients.

In female patients following a single intramuscular injection of PROSTAP 3, a mean plasma leuprorelin acetate concentration of 36.3ng/ml was observed at four hours. Leuprorelin acetate appeared to be released at a constant rate following the onset of steady state levels during the third week after dosing and mean levels then declined gradually to near the lower limit of detection by 12 weeks. The initial peak, followed by the rapid decline to a steady state level, was similar to the release pattern seen with the monthly preparation.

The metabolism, distribution and excretion of leuprorelin acetate in humans have not been fully determined.

In children:
Figure 1 presents the leuprorelin serum levels in children during the first 6 months of treatment following s.c. administration of leuprorelin acetate 3-month depot (two injections).

From the first injection, the leuprorelin serum levels increase reaching maximal serum levels at month 4 (294.79 pg/ml ± 105.42) and slightly decrease until month 6 (229.02 pg/ml ± 103.33).

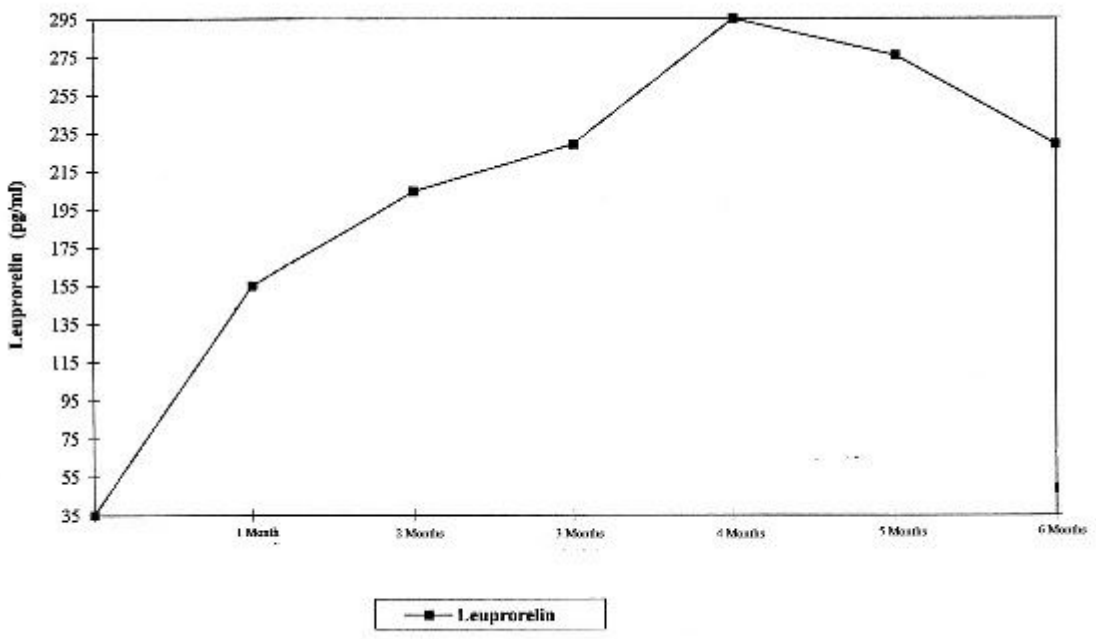

Figure 1: Leuprorelin serum levels during the first six months of treatment with the leuprorelin acetate 3-month depot formulation (two s.c. injections) (n=42-43)

5.3 Preclinical safety data

Animal studies have shown that leuprorelin acetate has a high acute safety factor. No major overt toxicological problems have been seen during repeated administration. Whilst the development of pituitary adenomas has been noted in chronic toxicity studies at high doses in some animal species, this has not been observed in long-term clinical studies. No evidence of

mutagenicity or teratogenicity has been shown. Animal reproductive studies showed increased foetal mortality and decreased foetal weights reflecting the pharmacological effects of this GnRH agonist.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Poly (D-L lactic acid)
Mannitol (E421)

Solvent
Carmellose Sodium
Mannitol (E421)
Polysorbate 80
Acetic Acid, glacial
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years unopened.

Once re-constituted with sterile solvent, the suspension should be administered immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.

6.5 Nature and contents of container

One dual chamber pre-filled syringe containing 11.25mg leuprorelin acetate in the front chamber and 1 ml of aqueous sterile solvent in the rear chamber.

1 x 23 gauge syringe needle fitted with safety device
1 x syringe plunger

6.6 Special precautions for disposal and other handling

Prepare the injectable suspension at the time of use and, after reconstituting, use immediately. Always ensure the safety device to prevent needle-stick injury is deployed after injection. For single use only. Discard any unused content. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Takeda Products Ireland Ltd
6th Floor
South Bank House
Barrow Street
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th April 2011

Date of last renewal: 8th April 2016

10 DATE OF REVISION OF THE TEXT

January 2026