Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

PROSTAP 6 DCS 30 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 30 mg leuprorelin acetate

When reconstituted with Sterile Solvent, the suspension contains 30 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) Metastatic prostate cancer
(ii) Locally advanced prostate cancer, as an alternative to surgical castration
(iii) As an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer
(iv) As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression

(See Section 5.1)

4.2 Posology and method of administration

Posology

Prostate Cancer: The recommended dose is 30 mg presented as a six month depot injection and administered as a single subcutaneous injection at intervals of six months. The majority of patients will respond to this dosage. PROSTAP 6 therapy should not be discontinued when remission or improvement occurs. As with other drugs administered regularly by injection, the injection site should be varied periodically.

Response to PROSTAP 6 therapy should be monitored by clinical parameters and by measuring prostate-specific antigen (PSA) and testosterone serum levels. Clinical studies with leuprorelin acetate 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 by 2-4 weeks. Once attained, castrate levels were maintained as long as drug therapy continued. If a patient's response appears to be sub-optimal, then it would be advisable to confirm that serum testosterone levels have reached or are remaining at castrate levels. 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.

Elderly: As above.

Children (under 18 years): Prostap 6 is not recommended in children due to insufficient data on safety and efficacy in this patient group.

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

PROSTAP 6 injectable suspension must be prepared at the time of use and, after reconstitution, used immediately.

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.

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.

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.

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. These symptoms usually subside on continuation of therapy. "Flare" may manifest itself as systemic or neurological symptoms in some cases.

In order to reduce the risk of flare, an anti-androgen may be administered beginning 3 days prior to leuprorelin therapy and continuing for the first two to three weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone. If an anti-androgen is used over a prolonged period, due attention should be paid to the contra-indications and precautions associated with its extended use.

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 the lower extremities and paraesthesia (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.

Bone mineral loss:
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).

In patients at risk, the additional administration of a bisphosphonate may represent a prophylactic measure against such bone demineralization.

Epidemiological data have shown that androgen deprivation therapy 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 the link between treatment with GnRH analogues and an increase in cardiovascular mortality.

Patients at high risk for metabolic or cardiovascular diseases should be appropriately monitored. Diabetic patients may require more frequent monitoring of blood glucose during treatment with PROSTAP 6.

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 leuprorelin acetate.

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 6.

Precautions

Patients with urinary obstruction and patients with metastatic vertebral lesions should begin PROSTAP therapy under close supervision for the first few weeks of treatment.

PROSTAP 6 contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per injection, that is to say it is essentially 'sodium free'.

4.4 Special warnings and precautions for use

PROSTAP 6 injectable suspension must be prepared at the time of use and, after reconstitution, used immediately.

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.

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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.
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In order to reduce the risk of flare, an anti-androgen may be administered beginning 3 days prior to leuprorelin therapy and continuing for the first two to three weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone. If an anti-androgen is used over a prolonged period, due attention should be paid to the contra-indications and precautions associated with its extended use.

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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.

Precautions

Patients with urinary obstruction and patients with metastatic vertebral lesions should begin PROSTAP therapy under close supervision for the first few weeks of treatment.

PROSTAP 6 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 6 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 6 is not indicated for use in women.

4.7 Effects on ability to drive and use machines

Prostap 6 can influence the ability to drive and use machines due to visual disturbances and dizziness.

4.8 Undesirable effects

Side effects with PROSTAP 6 are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels.

The following table lists 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)).

Tabulated list of adverse reactions

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)		anaphylactic reactions	
Metabolism and nutrition disorders	weight increase	decreased appetite	weight loss	abnormal glucose tolerance, which may affect diabetic control		metabolic syndrome (including hypertension, dyslipidemia, insulin resistance)
Metabolic disorders						Hepatic steatosis
Psychiatric disorders		insomnia, depression (see Section 4.4), mood changes				
Nervous system disorders		headache (occasionally severe), paraesthesia		dizziness	pituitary apoplexy (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		hypertension, hypotension			pulmonary embolism
Gastrointestinal disorders		nausea, vomiting	diarrhoea			
Hepatobiliary disorders		hepatic function test abnormal (usually transient)				hepatic function abnormal, (including jaundice)

Skin and subcutaneous tissue disorders	hyperhidrosis					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		arthralgia, muscle weakness				reduction in bone mineral density, osteoporosis (including spinal fracture, see Section 4.4), myalgia
Respiratory, thoracic and mediastinal disorders						interstitial lung disease
Reproductive system and breast disorders	libido decreased, erectile dysfunction, testicular atrophy	gynaecomastia				
General disorders and administration site conditions	fatigue, injection site reaction such as induration, erythema, pain, swelling	oedema peripheral		specific injection site reactions such as abscesses, nodules, ulcers and necrosis		

In cases where a "tumour flare" occurs after PROSTAP 6 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.

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 overdosage, 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 6 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 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.

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 is inactive when given orally.

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. 48% of patients included had locally advanced disease (T3N0M0), 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 and stabilising at a value below the castration threshold. The decline in serum PSA mirrored that of serum testosterone in both groups.

In an open, prospective clinical trial involving 205 patients receiving 3.75 mg leuprorelin on a monthly basis as treatment for metastatic prostate cancer, the long-term efficacy and safety of leuprorelin 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 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 LHRH analogues compared with patients treated with orchidectomy.

In another randomised, open-label, multi-centre comparative trial, leuprorelin 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 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 (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 in this setting.

In patients with metastatic castration resistant prostate cancer, clinical studies have shown benefit from the addition of secondary agents to treatment with LHRH agonists such as leuprorelin. Androgen deprivation therapy (ADT) is generally continued in conjunction with secondary therapies after progression on the initial ADT regimen.

5.2 Pharmacokinetic properties

Leuprorelin acetate is well absorbed after subcutaneousinjections. It binds to the luteinising hormone releasing hormone (LHRH) receptors and is rapidly degraded. An initially high plasma level of leuprorelin peaks at around 3 hours after a PROSTAP 6 subcutaneous injection, followed by a decrease to maintenance levels in 7 to 14 days.

Serum levels of leuprorelin rise quickly with a subsequent decrease to a plateau within a few days. Within 1.8 hours the mean maximum serum levels of 102 ng/ml were attained. In the plateau phase detectable serum levels were found up until >26 weeks after administration. In some patients, leuprorelin levels have been observed for up to 30 weeks. The maximum time to suppression of testosterone was found to be 28 days for responders and up to 35 days for non-responders.

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

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 fetal mortality and decreased fetal weights reflecting the pharmacological effects of this LHRH 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 30mg 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

PA2229/009/002

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