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: contains 30 mg leuprorelin acetate

Solvent: Solvent contains approximately 0.4 mg (<1mmol sodium (as carmellose sodium)).

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 clear, 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 usual 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) 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 acid phosphatase 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

The pre-filled syringe of PROSTAP 6 microsphere powder should be reconstituted immediately prior to administration by subcutaneous injection.

To prepare for injection, screw the plunger rod into the end stopper until the end stopper begins to turn.

Remember to check if the needle is tight by twisting the needle cap clockwise. Do not overtighten.

Holding the syringe upright, release the diluents by SLOWLY PUSHING the plunger until the middle stopper is at the blue line in the middle of the barrel.

NOTE: Pushing the plunger rod quickly or over the blue line will cause leakage of the suspension from the needle.

Gently tap the syringe on the palm keeping the syringe upright to thoroughly mix the particles to form a uniform suspension. The suspension will appear milky.

NOTE: Avoid hard tapping to prevent the generation of bubbles.

Remove the needle cap and advance the plunger to expel the air from the syringe.

At the time of injection, check the direction of the safety device (with round mark face up) and inject the entire contents of the syringe subcutaneously as you would for a normal injection

Withdraw the needle from the patient. Immediately activate the safety device by pushing the arrow forward with the thumb or finger until the device is fully extended and a CLICK is heard or felt.

NOTE: The suspension settles out very quickly following reconstitution and therefore the product should be mixed and used immediately.

4.3 Contraindications

Hypersensitivity to the active substance, any of the excipients (listed in section 6.1) or to synthetic gonadotrophins releasing hormone (Gn-RH) or Gn-RH derivatives.

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

4.4 Special warnings and precautions for use

As would be expected with this class of drug, aggravation of diabetes may occur, therefore diabetic patients may require more frequent monitoring of blood glucose during treatment with Prostap 6.

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 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.

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 ureteric obstruction or spinal cord compression should be considered carefully and closely supervised in the first few weeks of treatment. These patients should be considered for prophylactic treatment with anti-androgens. Should urological/neurological complications occur, these should be treated by appropriate specific measures.

The resulting hypogonadism, commonly observed under long term therapy with GnRH analogues or orchiectomy, may lead to the onset of osteoporosis with the increased risk of bone fracture. However, the development of osteoporosis due to hypogonadism is secondary to an increase in cortisol levels, and is more pronounced after orchiectomy

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

Epidemiological data have shown that during androgen deprivation therapy changes in the metabolic condition (e.g. reduction in glucose tolerance or aggravation of pre-existing diabetes) as well as an increased risk for cardiovascular diseases may occur. 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.

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.

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 benefit risk ratio including the potential for Torsade de pointes prior to initiating 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.

4.5 Interaction with other medicinal products and other forms of interaction

None have been reported.

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. Their incidences 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)).

Blood and lymphatic system disorders:
Uncommon: as with other medicinal products of this class, anaemia has been reported

Immune system disorders:
Uncommon: general allergic reactions including fever/chills, hypersensitivity reactions including rash, pruritis, urticaria and rarely, wheezing
Very rare: anaphylactic reactions

Metabolism and nutrition disorders:
Very common: weight gain
Common: anorexia
Uncommon: weight loss
Rare: alteration of glucose tolerance which may affect diabetic control

Psychiatric disorders:
Common: Mood changes, depression

Nervous system disorders:
Common: headache (occasionally severe)
Rare: dizziness
Very rare: pituitary apoplexy has been reported after administration of both short-and long acting GnRH agonists
Not known: paralysis, seizure

Vascular disorders:
Very common: hot flushes
Uncommon: hypertension, hypotension
Not known: pulmonary embolism

Gastrointestinal disorders:
Common: nausea, vomiting
Uncommon: diarrhoea

Musculoskeletal, connective tissue and bone disorders:
Common: muscle weakness, arthralgia
Not known: reduction in bone mass which may occur with the use of GnRH agonists, spinal fracture, myalgia

Reproductive system and breast disorders:
Very common: impotence, decreased libido, orchiatrophy
Common: gynaecomastia

General disorders and administration site conditions:
Very common: sweating, fatigue
Common: peripheral oedema, insomnia, paraesthesia
Rare: reactions at the injection site, e.g., induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis have been reported rarely

Cardiac disorders:
Not known: palpitations, QT prolongation (see sections 4.4 and 4.5)

Eye disorders:
Not known: visual disturbances

Hepatobiliary disorders:
Not known: hepatic dysfunction, jaundice

Respiratory, Thoracic and Mediastinal Disorders
Not known: interstitial lung disease

Investigations:
Common: increases in liver function test values (usually transient)
Not known: changes in blood lipids, thrombocytopenia, leucopenia

In cases where a "tumour flare" occurs after PROSTAP 6 therapy, an exacerbation may occur in any symptoms or signs due to disease, for example, bone pain, urinary obstruction etc. These symptoms subside on continuation of therapy. (see Special Warnings and Precautions for Use Section 4.4).

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, 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 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 subcutaneous injections. 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 measured. 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

Not applicable

6.3 Shelf life

3 years unopened

Once reconstituted with sterile solvent, the suspension should be administered immediately.

6.4 Special precautions for storage

Do not store above 25^{o}C.

Do not refrigerate or freeze.

6.5 Nature and contents of container

One dual chamber pre-filled syringe containing 30 mg 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

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.
First Floor,
3013 Lake Drive,
Citywest Business Campus,
Dublin 24

8 MARKETING AUTHORISATION NUMBER(S)

PA 2229/009/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08/04/2011
Date of last renewal: 08/04/2016

10 DATE OF REVISION OF THE TEXT

09/06/2018