Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

PROSTAP 3, 11.25 mg, Powder and Solvent for Prolonged- release Suspension for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 11.25 mg leuprorelin acetate (equivalent to 10.72 mg base).
After reconstitution, the vial contains 5.63 mg/ml leuprorelin acetate.
The resulting suspension also contains approx 0.8mg (<1mmol) sodium (as carmellose sodium)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

Powder: A sterile, lyophilized, white, odourless, microsphere powder.

Solvent: A clear, odourless, slightly viscous, 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 oestrogen 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.

4.2 Posology and method of administration

Dosage:

Male adults: The usual 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 may be monitored by clinical parameters and by measuring serum levels of testosterone and acid phosphatase. 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 acid phosphatase levels sometimes occur early in the treatment period but usually return to normal or near normal values by the 4^{th} week of treatment.

Female Adults: Treatment should be initiated during the first 5 days of the menstrual cycle.

For management of endometriosis the recommended dose is 11.25 mg administered as a single subcutaneous or intramuscular injection every 3 months for a period of 6 months.

For the 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.

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

Elderly: As for adults

Children: Safety and efficacy in children have not been established.

Administration:

The vial of PROSTAP 3 microsphere powder should be reconstituted immediately prior to administration by subcutaneous or intramuscular injection. Remove flip-cap vial of PROSTAP 3 powder and cap from pre-filled syringe containing 2ml Sterile Solvent. Ensure 23 gauge needle is fixed securely by screwing needle hub onto the syringe and inject whole contents of syringe into vial of PROSTAP 3 Powder using an aseptic technique. Remove the syringe/needle and keep aseptic. Shake the vial gently for 15-20 seconds to produce a uniform cloudy suspension of PROSTAP 3.

Immediately draw up suspension into syringe taking care to exclude air bubbles. Change the needle on syringe using another 23 gauge needle if the suspension is to be administered subcutaneously or alternatively a 21 gauge needle for intramuscular administration. Having cleaned an appropriate injection site and ensured that the needle is fixed securely, administer the suspension by subscutaneous or intramuscular injection taking care not to enter a blood vessel. Apply sterile dressing to the injection site if required.

The injection should be given as soon as possible after mixing. If any settling of suspension occurs in vial or syringe, re-suspend by gentle shaking and administer immediately.

As with other drugs administered chronically by injection, the injection site should be varied periodically.

No other fluid can be used for reconstitution of PROSTAP 3 Powder.

4.3 Contraindications

Hypersensitivity to any of the ingredients or to synthetic GnRH or GnRH 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.

4.4 Special warnings and precautions for use

Development or aggravation of diabetes may occur, therefore 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, hypotension and worsening of depression have been reported.

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. For instance, in patients with vertebral metastases, neurological problems such as weakness and/or paraesthesia of the lower limbs may occur. In patients with urinary obstruction or haematuria, worsening of urinary symptoms may occur. 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 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.

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.

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.

Women: Since menstruation should stop with effective doses of PROSTAP, the patient should notify her physician if regular menstruation persists. Spotting/breakthrough bleeding may occur with Prostap treatment.

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.

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.

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

The induced hypo-oestrogenic 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-oestrogenaemia is proportional to time and, consequently, is the event responsible for limiting the duration of therapy to 6 months. The level of bone loss seen with LHRH 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

None have been reported.

4.6 Fertility, pregnancy and lactation

PROSTAP 3 is contraindicated for use during pregnancy.

Pregnancy: Safe use of leuprorelin acetate in pregnancy has not been established clinically. Before starting treatment with PROSTAP 3, pregnancy must be excluded. 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.

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 appraised of this evidence and the potential for an unknown risk to the foetus.

4.7 Effects on ability to drive and use machines

The ability to drive and use machines may be impaired due to visual disturbances and dizziness.

4.8 Undesirable effects

Very rare cases of pituitary apoplexy have been reported following initial administration in patients with pituitary adenoma.

Side effects seen with PROSTAP 3 are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels. Adverse events which have been reported infrequently include peripheral oedema, pulmonary embolism, hypertension, palpitations, fatigue, muscle weakness, diarrhoea, nausea, vomiting, anorexia, fever/chills, headache (occasionally severe), hot flushes, arthralgia, myalgia, dizziness, insomnia, depression, paraesthesia, visual disturbances, weight changes, hepatic dysfunction, jaundice, increases in liver function test values (usually transient) and irritation at the injection site. Changes in blood lipids and alteration of glucose tolerance have also been reported which may affect diabetic control. Thrombocytopenia and leucopenia have been reported rarely. Hypersensitivity reactions including rash, pruritus, urticaria and, rarely, wheezing or interstitial pneumonitis have also been reported. Anaphylactic reactions are rare.

Spinal fracture, paralysis, hypotention and worsening of depression have been reported *(see 'Special Warnings and Precautions for Use' section 4.4).*

A reduction in bone mass may occur with the use of GnRH agonists.

Men: In cases where a "tumour flare" occurs after PROSTAP 3 therapy, an exacerbation may occur in any symptoms or signs due to disease, for example, bone pain, urinary obstruction, weakness of lower extremities and paresthesia. These symptoms subside on continuation of therapy.

Impotence and decreased libido will be expected with PROSTAP 3 therapy.

The administration of PROSTAP 3 is often associated with hot flushes and sometimes sweating.

Orchiatrophy and gynaecomastia have been reported occasionally.

Women: Those adverse events occurring most frequently with PROSTAP 3 are associated with hypo-oestrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe), and vaginal dryness. Oestrogen levels return to normal after treatment is discontinued. Breast tenderness or change in breast size may occur occasionally. Hair loss has also been reported occasionally.

The induced hypo-oestrogenic state results in a loss in bone density over the course of treatment, some of which may not be reversible *(see Special warnings and special precautions for use).*

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.

4.9 Overdose

There is no clinical experience with the effects of an acute overdose of PROSATP 3. 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

PROSTAP 3 is a synthetic nonapeptide analogue of naturally occurring gonadotrophin releasing hormone (GnRH), which possesses greater potency than the natural hormone. Prostap 3 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.

PROSTAP 3 is inactive when given orally.

5.2 Pharmacokinetic properties

Prostap 3 is well absorbed after subcutaneous injection. It binds to the luteinising hormone releasing hormone (LHRH) receptors and is rapidly degraded.

In male patients, an initially high plasma level of leuproreline 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 concentration of 36.3ng/ml was observed at four hours.

Leuprorelin 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.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Poly (D-L lactic acid)
Mannitol

Solvent:

Carmellose sodium
Mannitol
Polysorbate 80
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 3 years
Use immediately after reconstitution.

6.4 Special precautions for storage

Store below 25˚C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Colourless, Type I glass vial with rubber closure, aluminium seal and polypropylene cap, containing microsphere powder.
Colourless, Type I glass, prefilled syringe containing 2 ml of Sterile Solvent.

One carton pack contains one vial of powder, one pre-filled syringe, two 23 gauge needles and two injection site swabs.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused content. Prostap 11.25mg is reconstituted with 2ml Sterile Solvent to produce a uniform cloudy suspension to be administered by subcutaneous or intramuscular injection.

See section 4.2.

7 MARKETING AUTHORISATION HOLDER

Takeda UK Limited
Takeda House
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Wooburn Green
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