Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

PROSTAP SR 3.75 mg Powder and Solvent for prolonged-release suspension for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3.75 mg leuprorelin acetate (equivalent to 3.57 mg leuprorelin).

When reconstituted as directed, the resulting suspension contains 3.75 mg/ml leuprorelin acetate.

The resulting suspension also contains approx 0.4 mg (<1mmol) sodium (as carmellose sodium).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

Powder: A sterile, lyophilised, white, odourless microsphere powder.
Solvent: A clear odourless, slightly viscous, sterile solvent.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Management of prostatic carcinoma for which a suppression of testosterone is indicated.
2. Management of oestrogen dependent gynaecological disorders including the management of pain and lesions associated with endometriosis.
3. Preoperative management of uterine fibroids to reduce their size and associated bleeding.
4. Endometrial preparation prior to intrauterine surgical procedures including endometrial ablation or resection.

4.2 Posology and method of administration

Dosage

Male adults

The recommended dose is 3.75mg administered as a single subcutaneous or intramuscular injection every month. The majority of patients will respond to a 3.75mg dose. PROSTAP therapy should not be discontinued when remission or improvement occurs.

Response to PROSTAP 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 about 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 4th week of treatment.

Female adults

Treatment should be initiated during the first five days of the menstrual cycle. For the management of endometriosis the recommended dose is 3.75 mg administered as a single subcutaneous or intramuscular injection every month for a period of 6 months.

For the preoperative management of uterine fibroids the recommended dose is 3.75 mg administered as a single subcutaneous or intramuscular injection every month usually for 3-4 months for a maximum of 6 months. For endometrial preparation prior to intrauterine surgery the recommended dose is a single 3.75 mg subcutaneous or intramuscular injection during days 3 to 5 of the menstrual cycle, 5-6 weeks prior to surgery.

In women receiving GnRH analogues for the treatment of endometriosis, the addition of hormone replacement therapy (HRT - an oestrogen and progestogen) has been shown to reduce bone mineral density loss and vasomotor symptoms. Therefore if appropriate, HRT should be co-administered with PROSTAP taking into account the risks and benefits of each treatment. If PROSTAP is co-administered with HRT, treatment may be extended for up to 12 months in women with chronic symptomatic endometriosis.

Elderly

As for adults.

Children

Safety and effectiveness in children have not been established.

Administration

The vial of PROSTAP SR microcapsule powder should be reconstituted immediately prior to administration by subcutaneous or intramuscular injection. Remove flip-cap from vial of PROSTAP SR Powder and cap from pre-filled syringe of Sterile Solvent. Ensure 23 gauge needle is fixed securely by screwing the needle hub onto the syringe and inject whole contents of syringe into a vial of PROSTAP SR Powder using an aseptic technique. Remove the syringe/needle and keep aseptic. Shake vial gently for 15-20 seconds to produce a uniform cloudy suspension of PROSTAP. Immediately draw up suspension into syringe taking care to exclude air bubbles. Change the needle on syringe using a 23 gauge needle if the suspension is to be administered subcutaneously or alternatively a 21 gauge needle for intramuscular administration.

Having cleaned appropriate injection site, and ensured that the needle is fixed securely, administer the suspension by subcutaneous or intramuscular injection as appropriate, taking care not to enter a blood vessel. Apply sterile dressing to 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 gently shaking and administer immediately.

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

No other fluid can be used for reconstitution of PROSTAP SR 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 is contraindicated in women who are or may become pregnant while receiving the drug. PROSTAP should not be used in women who are breast-feeding 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.

Hepatic dysfunction and jaundice with elevated liver enzyme 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 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 six weeks. Failure to do so requires reassessment of patient selection or compliance.

In the initial stages of therapy a transient rise in testosterone levels may occur. This may be associated with a flare or exacerbation of the tumour growth and a temporary deterioration in the patient's condition. This may lead to neurological or systemic effects. These symptoms subside on continuation of therapy.

In order to protect against the consequences of the flare which may occur in a minority of patients during the early response to PROSTAP, an anti-androgen, e.g. cyproterone acetate 300 mg daily, may be administered beginning at least three days before PROSTAP therapy and continuing for at least the first three weeks of treatment. If an anti-androgen is used over a period exceeding two weeks, due attention should be paid to the contraindications and precautions associated with its extended use.

Patients at risk of ureteric obstruction or spinal 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.

Women

Since menstruation should stop with effective doses of PROSTAP, the patient should notify her physician if regular menstruation persists.

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 an ovarian mass, either visually by laparoscopy or by ultrasonography or other investigative techniques as appropriate, before PROSTAP therapy is instituted.

PROSTAP 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 small 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 generally accepted level of bone loss with LHRH analogues such as PROSTAP is 5%. In clinical studies the levels varied between 2.3% and 15.7% depending on the method of measurement. During one six-month treatment period, this bone loss should not be important.

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 anti-convulsants or corticosteroids, PROSTAP therapy may pose an additional risk. In these patients, the risk and benefits must be weighed carefully before therapy with PROSTAP is instituted.

In women receiving GnRH analogues for the treatment of endometriosis, the addition of HRT (an oestrogen and progestogen) has been shown to reduce bone mineral density loss and vasomotor symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

None have been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use of leuprorelin acetate in pregnancy has not been established clinically. Before starting treatment with PROSTAP, pregnancy must be excluded. When used monthly at the recommended dose, PROSTAP usually inhibits ovulation and stops menstruation. Contraception is not ensured, however, by taking PROSTAP and therefore, patients should use non-hormonal methods of contraception during treatment.

Patients should be advised that if they miss successive doses of PROSTAP, 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

General

Very rare cases of pituitary apoplexy have been reported following inital adminstration in patients with pituitary adenoma.

Side effects seen with PROSTAP 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, hypotension 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 therapy, an exacerbation may occur in any symptoms or signs due to disease, for example, bone pain, urinary obstruction, weakness of the lower extremities and paraesthesia. These symptoms subside on continuation of therapy.

Other side effects include hot flushes, impotence and loss of libido. Orchiatrophy and gynaecomastia have been reported occasionally.

Women

Those adverse events occurring most frequently with PROSTAP 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 small loss in bone density over the course of treatment, some of which may not be reversible (see 'Special Warnings and Special Precautions for Use' section 4.4).

In women who have submucous fibroids there have been reports of severe bleeding following the administration of PROSTAP 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 PROSTAP. 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 is a synthetic nonapeptide analogue of naturally occurring gonadotrophin releasing hormone (GnRH) which possesses greater potency than the natural hormone. PROSTAP 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. Oestradiol levels will decrease to postmenopausal levels in premenopausal women within one month of initiating treatment.

The drug is well absorbed from the subcutaneous or intramuscular route, binds to lutinising hormone releasing hormone (LHRH) receptors and is rapidly degraded. In this dose form, an initial high level of leuprorelin in the plasma is achieved within 3 hours followed by a drop over 24-48 hours to maintenance levels of 0.3-0.8ng/ml and a slow decline thereafter. Effective levels persist for 30-40 days after a single dose.

PROSTAP is inactive when given orally.

5.2 Pharmacokinetic properties

Studies submitted show that single intramuscular or subcutaneous doses of leuprorelin acetate over the dose range 3.75 to 15mg results in detectable levels of leuprorelin for more than 28 days, good bioavailability, a consistent and predictable pharmacokinetic profile, and biological efficacy at plasma levels of less than 0.5ng/ml. The pharmacokinetic profile is remarkably similar to that seen in animal studies using the compound, with an initial high level of drug released from the microcapsules during reconstitution and injection followed by a plateau over a 2-3 week period before levels gradually become undetectable.

There appears to be no significant difference between the routes of administration (IM vs. SC) in biological effectiveness or pharmacokinetics.

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

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Gelatin
Copoly (DL-lactic acid/glycolic acid) 75:25 mol%
Mannitol (E421)

Solvent

Carmellose Sodium
Mannitol (E421)
Polysorbate 80
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

As packaged for sale: 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 a grey, siliconised butyl rubber closure, aluminium cap and polypropylene cover containing the microcapsule powder.

Colourless, Type I glass, pre-filled syringe containing 1ml of Sterile Solvent.

Each pack contains one vial, one syringe, two 23 gauge syringe needles, one 21 gauge needle 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 contents.

PROSTAP 3.75mg is reconstituted with 1ml Sterile Solvent to produce a white, uniform cloudy suspension.

For further information, see 'Posology and method of administration' section 4.2.

7 MARKETING AUTHORISATION HOLDER

Takeda UK Limited
Takeda House
Mercury Park
Wycombe Lane
Wooburn Green
High Wycombe
Buckinghamshire
HP10 0HH
UK

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