SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

SUPREFACT® 3-MONTH DEPOT implant

COMPOSITION

One implant consisting of three identical rods each containing 3,3 mg buserelin acetate (9,9 mg), equivalent to 9,45 mg buserelin base.

Excipient: Poly(D,L-lactide-co-glycolide) with a 75:25 ratio of lactide:glycolide.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 21.10 Trophic hormones

PHARMACOLOGICAL ACTION

SUPREFACT contains buserelin, an analogue of the natural gonadotropin-releasing hormone (GnRH, LH-RH) with a long duration of action. GnRH stimulates both synthesis and release of the gonadotropins LH and FSH. The latter then stimulates steroid biosynthesis in the gonads. Studies of the behaviour of the receptor sites both of gonadal LH-receptors and pituitary GnRH-receptors have shown that long-term stimulation leads at first to an increase but then to a reduction in the stimulability of both gonadotropins and sex-steroid levels. The dose-level and time interval between individual doses of GnRH are determinant factors for the receptor loss as indicated in animal studies. The suppressive effect is fully reversible.

Natural gonadorelin is bound to receptors for only a short time. It is degraded within 30 to 60 minutes by arylamidase and its activity thus abolished. The long-acting analogue, buserelin, has been developed for therapeutic use. Enzymatic degradation is inhibited by substitution of the amino acid, glycine, at two sites in the molecule. SUPREFACT is capable of inhibiting both gonadotropin release from the pituitary and gonadal steroid biosynthesis. The suppressive effect is reversible. The secretion of testosterone is suppressed to the castration range by controlled release of buserelin in the depot form.

The implant material undergoes slow biodegradation during the dose interval, and accelerated biodegradation at the end of three months.

INDICATIONS

Advanced prostatic cancer in which suppression of testosterone production is indicated.

CONTRAINDICATIONS

Hypersensitivity to buserelin acetate.

Efficacy of SUPREFACT has not been established after surgical removal of the testes or after treatment with oestrogen therapy.

WARNINGS AND SPECIAL PRECAUTIONS

It is strongly recommended that administration of an anti-androgen be started as adjunctive therapy about 5 days before starting treatment. This adjunctive therapy must be continued in parallel with SUPREFACT therapy for 3 to 4 weeks (see DOSAGE AND DIRECTIONS FOR USE and SIDE EFFECTS).

In patients with known metastases, e.g. of the spinal column, this adjunctive therapy with an anti-androgen is indispensable to prevent initial complications up to and including, for example, spinal compression and paralysis, arising from a transient activation of the tumour and its metastases (see DOSAGE AND DIRECTIONS FOR USE and SIDE EFFECTS).

Patients with a history of depression must be monitored carefully and treated if necessary (risk of recurrence or worsening of depression).

Particularly in patients with known risk factors for osteoporosis, periodic monitoring of bone mineral density (BMD) and use of preventative measures are recommended during therapy to prevent osteopenia/osteoporosis (risk of decreased bone density that may lead to osteoporosis and increased risk of bone fracture – see SIDE EFFECTS).

Published epidemiological studies suggest a relationship between SUPREFACT treatment and increased risk of cardiovascular disease (such as myocardial infarction, sudden cardiac death and stroke) and diabetes mellitus. These risks should be evaluated before initiating and during therapy, and patients should be monitored and treated accordingly.

In patients with hypertension, blood pressure must be monitored regularly (risk of deterioration of blood pressure levels).

In diabetic patients blood glucose levels must be checked regularly (risk of deterioration of metabolic control).

Due to testosterone suppression, SUPREFACT therapy may increase the risk of anaemia. Patients should be evaluated for this risk and managed accordingly.

QT prolongation: SUPREFACT 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 doctors should assess the benefit-risk ratio including the potential for Torsade de Pointes prior to initiating treatment with SUPREFACT. In case of QT prolongation, SUPREFACT treatment should be discontinued (see INTERACTIONS and SIDE EFFECTS).

Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. Certain adverse effects (e.g. dizziness – see SIDE EFFECTS) may impair the patient's ability to concentrate and react, and therefore, constitute a risk in situations where these abilities are of special importance (e.g. operating a vehicle or machinery). Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

INTERACTIONS

During treatment with SUPREFACT, the effect of antidiabetic medicines may be attenuated.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of SUPREFACT with medicines known to prolong the QT interval or medicines able to induce Torsade de Pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antidysrhythmic medicines, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated. In case of combination with such medicines, the QT interval should be closely monitored (see WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS).

DOSAGE AND DIRECTIONS FOR USE

SUPREFACT DEPOT is intended for long-term treatment of prostatic carcinoma.

The contents of an applicator (one implant consisting of 3 identical rods, equivalent to a total of 9,45 mg buserelin) are injected subcutaneously into the abdominal wall every 3 months. The 3-month interval between injections may, however, occasionally be extended by up to 3 weeks. The syringe with the implant should be kept horizontal before

injection. It is important to maintain a regular, three-monthly rhythm for the implant injections. The dosage interval may be shortened or extended by a few days.

It is strongly recommended that administration of an anti-androgen be started as adjunctive therapy about 5 days before starting treatment (see WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS).

This adjunctive therapy must be continued in parallel with SUPREFACT therapy for 3 to 4 weeks. After this time testosterone levels have usually fallen into the desired range in response to SUPREFACT.

In patients with known metastases, e.g. of the spinal column, this adjunctive therapy with an anti-androgen is indispensable to prevent initial complications up to and including, for example, spinal compression and paralysis, arising from a transient activation of the tumour and its metastases (see WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS).

The response to treatment may be monitored by measuring serum levels of testosterone, acid phosphatase and prostate-specific antigen (PSA). The testosterone level increases at the beginning of treatment and then decreases over a period of 2 weeks. After 2 to 4 weeks the testosterone levels reached are in the castrate range. These levels persist throughout the entire treatment period.

Local anaesthetic may be used before injection at the discretion of the patient or doctor.

The duration of the treatment is determined by the doctor.

Instructions for using the applicator:

To prevent the implant rods from falling out of the injection needle, hold the applicator in a vertical position until immediately prior to puncture, with the needle pointing upwards.

1. After opening the pack and removing the applicator from the wrapping, check that the implant rods are located in the window of the handle. If necessary, tap the protective cap on the needle lightly with the finger to reposition them in the window.
2. Disinfect the injection site in the area of the lateral abdominal wall. Then, after removing the protective case from the plunger, remove the cap from the injection needle.
3. Lift a fold of skin and insert the needle approximately 3 cm into the subcutaneous tissue, holding the applicator immediately prior to puncture in a horizontal position or with the tip of the needle pointed slightly upwards. Withdraw the applicator about 1 or 2 cm prior to injection of the implants.
4. Fully depressing the plunger, inject the implant rods into the subcutaneous tissue. Compress the puncture channel while withdrawing the needle, so that the implant rods are retained in the tissue.

5. To make certain that the three implant rods have been injected, check the tip of the plunger to see if it is visible at the tip of the needle.

SIDE-EFFECTS

The following side effects have been reported and frequency categorised as follows: Frequent, less frequent and frequency unknown (could not be estimated from data).

Neoplasms benign and malignant:

Less frequent: Pituitary adenomas were reported during treatment with SUPREFACT.

Blood and lymphatic system disorders:

Frequency unknown: Thrombocytopenia and leucopenia.

Immune system disorders:

Frequency unknown: Hypersensitivity reactions. These may manifest e.g. as reddening of the skin, itching, skin rashes (including urticaria) and allergic asthma with dyspnoea.

Less frequent: Hypersensitivity reactions that could lead to anaphylactic/anaphylactoid shock. In cases of anaphylactic/anaphylactoid reactions it may be necessary to remove the implant surgically.

Endocrine disorders:

Frequent: Loss of potency or libido (result of hormone deprivation).

Less frequent: Usually painless gynaecomastia.

Frequency unknown: At the beginning of treatment, a transient rise in serum testosterone level usually develops and may lead to a temporary activation of the tumour with secondary reactions such as:

- occurrence or exacerbation of bone pain in patients with bone metastases
- signs of neurologic deficit due to tumour compression with e.g. muscle weakness in the legs
- impaired micturition, hydronephrosis or lymphostasis
- thrombosis with pulmonary embolism.

Such reactions can be largely avoided when an anti-androgen is given concomitantly in the initial phase of SUPREFACT treatment (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS). However, even with concomitant anti-androgen therapy, a mild but transient increase in tumour pain as well as a deterioration in general well-being may develop in some patients.

Additionally, hot flushes and atrophy of the testes.

Metabolism and nutrition disorders:

Frequency unknown: Increased thirst, changes in appetite. Reduction in glucose tolerance. This may, in diabetic patients, lead to a deterioration of metabolic control (see WARNINGS AND SPECIAL PRECAUTIONS).

Psychiatric disorders:

Frequency unknown: Nervousness, emotional instability, feelings of anxiety.

Less frequent: In rare cases, depression may develop, or existing depression may worsen (see WARNINGS AND SPECIAL PRECAUTIONS).

Nervous system disorders:

Frequency unknown: Headache, dizziness, sleep disturbances, drowsiness, disturbances of memory and concentration.

Eye disorders:

Frequency unknown: Impaired vision (e.g. blurred vision), feeling of pressure behind the eyes.

Ear and labyrinth disorders:

Unknown: Tinnitus, hearing disorders.

Cardiac disorders:

Frequency unknown: Palpitations.

Vascular disorders:

Frequency unknown: Mild oedemas of the ankles and lower legs may occur. Deterioration in blood pressure levels in patients with hypertension (see WARNINGS AND SPECIAL PRECAUTIONS).

Gastrointestinal disorders:

Frequency unknown: Nausea, vomiting, diarrhoea, constipation.

Hepato-biliary disorders:

Frequency unknown: Changes in blood lipids, increase in serum levels of liver enzymes (e.g. transaminases), increase in bilirubin, weight changes (increase or decrease).

Skin and subcutaneous disorders:

Frequency unknown: Changes in scalp and body hair (increase or decrease).

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Musculoskeletal discomfort and pain. The use of SUPREFACT may be associated with decreased bone density and may lead to osteoporosis and an increased risk of bone fracture (see WARNINGS AND SPECIAL PRECAUTIONS). The risk of fracture increases with the duration of therapy.

General disorders and administration site conditions:

Frequent: Pain or local reactions at the injection site were observed in three percent of patients.

Frequency unknown: Tiredness.

Post-marketing:

Post-marketing experience with frequency not known:

SUPREFACT treatment may lead to QT prolongation (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdose may lead to signs and symptoms such as asthenia, headache, nervousness, hot flushes, dizziness, nausea, abdominal pain, oedemas of the lower extremities, and mastodynia. Local reactions at the injection site such as pain, haemorrhage and induration may occur.

Treatment is symptomatic and supportive.

IDENTIFICATION

One implant consisting of three identical creamy-coloured rods in a disposable applicator.

PRESENTATION

A carton containing a sterile, plastic, disposable applicator, sealed in a foil bag.

STORAGE INSTRUCTIONS

The sealed syringe must be stored at or below 25 °C in the original container. Only remove the syringe from the foil bag directly before use.

Do not use after the date of expiry.

Keep out of reach of children.

REGISTRATION NUMBER

32/21.10/0345

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd.

3 Sandown Valley Crescent,

South Tower, 1st Floor

Sandton, 2196, South Africa

Ethical assistance Line: +27 (0)11 784 0077

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date registered: 03 June 1999

Date revised: 06 June 2018