1 NAME OF THE MEDICINAL PRODUCT

Suprefact Depot 9.45 mg implant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe with three identical rod-shaped implants contains, as active ingredient, 9.9 mg buserelin acetate, equivalent to 9.45 mg buserelin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Implants
Each implant consists of three creamy-coloured rod-shaped implant.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Suprefact Depot is indicated in adults for the treatment of advanced hormone-dependent prostatic carcinoma. However, Suprefact Depot is not indicated after bilateral orchiectomy as there would be no further reduction in testosterone levels.

4.2 Posology and method of administration

Posology
Suprefact Depot is intended for the long-term treatment of advanced prostatic carcinoma.

Paediatric population
Suprefact Depot should not be used in children. The safety and efficacy of Suprefact Depot in children has not been established.

Method of administration
The contents of the syringe (three implant rods, equivalent to 9.45 mg buserelin) are injected subcutaneously into the abdominal wall every three months (see section 6.6). The three month interval between injections may, however, occasionally be extended by up to three weeks.

Before injection, the implant should be brought to room temperature and a local anaesthetic may be given.

It is recommended that administration of an anti-androgen is started as adjunctive therapy about 5 days before starting Suprefact Depot (see also section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance, LHRH analogues or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

It is recommended that administration of an anti-androgen is started as adjunctive therapy about 5 days before starting Suprefact Depot. This supplementary treatment must be continued in parallel with buserelin therapy for 3 – 4 weeks. After this time testosterone levels have usually fallen into the desired range in response to buserelin.

In patients with known metastases, e.g. of the spinal column, this adjunctive therapy with an anti-androgen is essential to prevent initial complications such as spinal compression and paralysis arising from a transient activation of the tumour and its metastases (see also section 4.8).

The response to treatment can be evaluated by measuring the serum levels of prostate-specific antigen (PSA) and testosterone. The testosterone levels increase at the start of treatment and then decrease during a period of two weeks. After 2 - 4 weeks the testosterone levels have decreased to a castration level. Absence of clinical improvement or of changes in PSA in the face of adequate testosterone suppression is diagnostic of hormone-insensitivity of the tumour.

Patients with known metastases of the spinal column or those at risk of neurological complications or urinary obstruction should be closely monitored during the first weeks of therapy, if start of treatment is not accompanied by concomitant anti-androgen administration.

Published epidemiological studies suggest a relationship between gonadotropin-releasing hormone (GnRH) agonist 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 (see section 4.8).

In patients with hypertension, regular monitoring of blood pressure is recommended (risk of deterioration of blood pressure control).

<u>QT prolongation</u>

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 Suprefact Depot.

In some patients treated with GnRH-agonists, change in glucose tolerance is observed (see section 4.8). In diabetic patients it is recommended that blood glucose levels are checked regularly (risk of deterioration of metabolic control).

Due to testosterone suppression, GnRH agonist therapy may increase the risk of anaemia. Patients should be evaluated for this risk and managed accordingly (see section 4.8).

The use of LHRH-agonists may be associated with decreased bone density and may lead to osteoporosis and an increased risk of bone fracture (see section 4.8). Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with anticonvulsants or corticosteroids or a family history of osteoporosis). It is recommended to periodically monitor bone miniral density (BMD) and use preventative measures during therapy to prevent osteopenia/osteoporosis.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as buserelin. Patients should be informed accordingly and treated as appropriate if symptoms occur. Patients with a history of depression must be monitored carefully and treated if necessary (risk of recurrence or worsening of depression).

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been conducted.
During treatment with buserelin, the effect of antidiabetic agents may be attenuated (see also section 4.8).

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Suprefact Depot 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

Due to the indication, Suprefact Depot must not be administered in women.

4.7 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) 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 or in similar situations). Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

4.8 Undesirable effects

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

- occurrence or exacerbation of bone pain in patients with 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.

These reactions can be largely avoided when an anti-androgen is given concomitantly in the initial phase of buserelin treatment (see also section 4.4).

List of adverse reactions
Frequencies are defined using the following MedDRA convention as: very common (≥1/10); common (≥1/100,<1/10); uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Neoplasm benign, malignant and unspecified (including cysts and polyps)
Very rare: cases of pituitary adenomas enlargement were reported during treatment with LHRH-agonists-including buserelin**.** Even with concomitant anti-androgen therapy, mild transient increase in tumour pain.

Blood and lymphatic system disorders:
Very rare: thrombopenia, leucopenia

Immune system disorders:
Uncommon: hypersensitivity reactions such as reddening of the skin, itching, rashes (including urticaria)
Rare: severe hypersensitivity reactions with bronchospasm and allergic asthma with dyspnoea as well as, in isolated cases lead to anaphylactic/anaphylactoid shock.
In cases of anaphylactic/anaphylactoid reactions it may be necessary to remove the implant surgically.

Metabolism and nutrition disorders:
Very rare: increased thirst, changes in appetite, reduction in glucose tolerance (which in diabetic patients may lead to a deterioration of metabolic control).

Psychiatric disorders:
Common: loss of libido; mood changes and depression (long term use)
Uncommon: mood changes and depression (short term use)
Rare: nervousness, emotional instability, feeling of anxiety

Nervous system disorders:
Common: headache
Uncommon: drowsiness, dizziness
Rare: sleep disturbances, disturbances in memory and concentration
In isolated cases, paraesthesia has been observed with other presentations of buserelin.

Eye disorders:
Very rare: impaired vision (e.g. blurred vision), and a feeling of pressure behind the eyes

Ear and labyrinth disorders:
Very rare: tinnitus, hearing disorders

Cardiac disorders:
Rare: palpitations
Post-marketing experience with frequency not known: QT prolongation (see sections 4.4 and 4.5)

Vascular disorders:

Common: hot flushes
Rare: deterioration in blood pressure levels in patients with hypertension

Gastrointestinal disorders:
Uncommon: constipation
Rare: Nausea, vomiting, diarrhoea

Skin and subcutaneous tissue disorders:
Rare: increase or decrease in scalp and body hair

Musculoskeletal and connective tissue disorders:
Very rare: musculoskeletal discomfort and pain.
The use of LHRH-agonists may be associated with decreased bone density and may lead to osteoporosis and an increased risk of bone fracture. The risk of skeletal fracture increases with the duration of therapy.

Reproductive system and breast disorders:
Common: loss of potency, atrophy of the testes
Uncommon: gynaecomastia (painless)

General disorders and administration site reactions:
Common: pain or other local reactions (e.g. reddening, swelling) at the injection site.
Uncommon: oedema (mild) round the ankles and lower parts of the legs, tiredness
Very rare: deterioration in general well-being

Investigations:
Uncommon: increase in serum liver enzyme levels (e.g. transaminases), increase or decrease in weight.
Rare: changes in blood lipids, increase in serum bilirubin

Most of the effects listed above are directly or indirectly related to the suppression of testosterone by buserelin (symptoms of androgen deficiency).

Pharmacoepidemiological information indicates that androgen deprivation may increase the risk for cardiovascular disease, diabetes mellitus and anaemia (frequencies unknown) (see 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Intoxication or overdose with buserelin has not been observed. The potential effects of buserelin overdose are expected to be similar to undesirable effects noted under normal use, such as asthenia, headache, nervousness, hot flushes, dizziness, nausea, abdominal pain, oedemas of the lower extremities, and mastodynia, as well as to local reactions at the injection site (see section 4.8).

Management

Therapy for overdose, if necessary, is directed to the symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotropin releasing hormone analogue
ATC code: L02AE01

Mechanism of action
Buserelin is a highly active analogue of the natural gonadotropin-releasing hormone (gonadorelin; GnRH, LHRH). The initial pharmacological effect of buserelin is to stimulate gonadotropin release and testosterone secretion. This is followed by a progressive decrease in testosterone into the castrate range.

While gonadotropin release is inhibited during continued treatment with buserelin, the secretion of the other pituitary hormones (growth hormone, prolactin, ACTH, TSH) is not directly influenced. The secretion of adrenal steroids remains unchanged.

In terms of removing testosterone stimulation of tumour tissue, buserelin is as effective as orchiectomy in the treatment of prostatic carcinoma.

5.2 Pharmacokinetic properties

Absorption and distribution
The release of buserelin from the implant is controlled by degradation of the polymer matrix. The release profile is biphasic; the initial release (t_{max}<1 day) is followed by a phase with a slow, steady release within the dosing interval of 3 months (total dose 9.9 mg). The bioavailability of the buserelin implant is approximately 50% following subcutaneous injection. The systemic exposure to buserelin is sufficient to cause suppression of testosterone into the castrate range throughout the dosing interval.

Buserelin circulates in serum predominantly in the unchanged form. Protein binding is about 15%. Based on preclinical data, buserelin accumulates preferably in the liver, kidneys and anterior lobe of the pituitary gland, which is the biological target organ.

Biotransformation
In vitro studies have shown that buserelin is inactivated by peptidases (pyroglutamyl peptidase and chymotrypsin-like endopeptidases) in the liver and kidneys. In the pituitary gland, receptor-bound buserelin is inactivated by membrane-located enzymes.

Elimination
Buserelin and its inactive metabolites are excreted renally and animal studies also indicate excretion into the bile.

5.3 Preclinical safety data

Preclinical findings can be related to known pharmacological and endocrinological effects of buserelin acetate. No genotoxicity has been shown in established *in vitro* or *in vivo* tests. In animal studies buserelin acetate implants have been shown to be locally well tolerated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poly (D,L-lactide-co-glycolide) with a molar quotient for lactide:glycolide of 75:25.

6.2 Incompatibilities

Not applicable as product is presented in a special applicator.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). May be stored at a maximum of 25 °C for up to 7 days.

6.5 Nature and content of container

Pre-filled syringe containing a rod-shaped implant consisting of three rods in a disposable applicator made of cellulose propionate and stainless steel sealed in a bag made of a polyethylene terephthalate, aluminium, low density polyethylene composite foil.

Pack sizes: 1 or 2 pre-filled syringes per package.

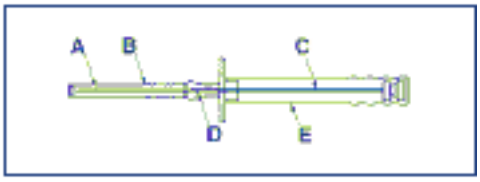
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for Handling

Allow the implant to reach room temperature prior to use.

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



A: Injection Needle

B: Protective cap of needle
C: Plunger
D: Implant
E: Protective cap of plunger

1. After opening the pack and removing the applicator from the wrapping, check that the implants 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. The applicator should be used immediately after opening the wrapping.

2. Disinfect the injection site in the area of the lateral abdominal wall. Then, after removing the protective case from the plunger (E), remove the cap from the injection needle (B).

3. Lift a fold of skin, and insert the needle approx. 3 cm (somewhat more than 1 inch) 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 to 2 cm prior to injection of the implants.

4. Fully depressing the plunger, inject the implants into the subcutaneous tissue. Compress the puncture channel while withdrawing the needle, so that the implants are retained in the tissue.

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

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 1997
Date of latest renewal: 30 April 2009

10 DATE OF REVISION OF THE TEXT

27 November 2023

Detailed information on this medicinal product is available on the website of {name of MS/Agency}