Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Suprefact 1 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains as active ingredient, 1.05 mg buserelin acetate, equivalent to 1 mg buserelin.

Each multidose vial of Suprefact Injection contains 5.5mg buserelin (equivalent to 5.78mg buserelin acetate) in 5.5ml solution for injection.

Excipients: Also contains 10.000mg benzyl alcohol and 2.255mg sodium per ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear, colourless, sterile solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

(1) For the treatment of advanced prostatic carcinoma.

(2) Pituitary desensitisation prior to ovulation induction regimens using gonadotrophins (subcutaneous administration).

4.2 Posology and method of administration

To ensure that the desired effect it is very important that the individual doses be administered at approximately equal intervals. Patients must adhere to these intervals conscientiously.

Dosage is generally based on the following guidelines.

(1) Prostatic carcinoma

Initiation of therapy: is most conveniently carried out in hospital; 0.5 ml Suprefact injection should be injected subcutaneously at 8 hourly intervals for 7 days.

Maintenance therapy: on the 8th day of treatment the patient is changed to intranasal administration of Suprefact. (See manufacturer's instructions).

(2) For adjunctive use in ovulation induction (subcutaneous use only).

The total daily subcutaneous dose for this indication is 0.5 mg buserelin, given in one injection. Treatment should start in the early follicular phase (day 1 or 2) or, provided the existence of an early pregnancy has been excluded, in the mid-luteal phase (approx. day 21).
It should continue at least until down-regulation is achieved (serum oestradiol < 50 ng/l and serum progesterone < 1 micrograms/l). This will usually take about 2-3 weeks.

In some patients dosages up to 2 x 0.5 mg may be required to achieve these levels. When down-regulation is achieved, stimulation with gonadotrophin is commenced while the dosage of buserelin is maintained.

At the appropriate stage of follicular development, gonadotrophin and buserelin are stopped and human chorionic gonadotrophin (hCG) is given to induce ovulation.

Treatment monitoring, oocyte transfer and fertilisation techniques are performed according to the normal practice of the individual clinic.

Luteal support with hCG or progesterone should be given as appropriate.

4.3 Contraindications

Suprefact should not be used if the tumour is found to be insensitive to hormone manipulation or after surgical removal of the testes. Suprefact injection must not be administered in patients with hypersensitivity to buserelin or if applicable, to any of the excipients.
Suprefact Injection must not be administered in case of pregnancy. (see under section 4.6 Pregnancy and Lactation.)
Concerning use in breast-feeding women (see under section 4.6 Pregnancy and Lactation.)

4.4 Special warnings and precautions for use

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

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

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 Suprecur.

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 mineral density (BMD) and use preventative measures during therapy to prevent osteopenia/osteoporosis.

In some patients treated with GnRH-agonists, change in glucose tolerance is observed (see section 4.8).

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

For the treatment of gynaecological disorders like Endometriosis:
Oral contraceptives must be discontinued before starting treatment. For safety reasons it is recommended that alternative (non-hormonal) methods of contraception (e.g. condoms) be used during treatment.

To exclude pre-pregnancy at the beginning of therapy, it is recommended that the treatment be started on the first or second day of menstruation, if there is any doubt a pregnancy test is recommended.

It is not expected that pregnancy will occur during the course of treatment if the recommended dose is taken regularly. However, if treatment is interrupted ovulation and pregnancy may occur.

If pregnancy does occur, treatment with buserelin must be discontinued immediately and a physician must be informed.

Repeated courses of treatment must only be administered after careful review of the risk/benefit ratio by the attending physician since the possibility of additive effects on bone mass (reduction in bone mass) cannot be excluded.

A course of treatment with buserelin lasting several months may lead to loss of bone mineral content. For this reason the recommended **maximal** duration of treatment should be 6 months.

In case of liver or kidney functions disturbances, the effect of buserelin may be prolonged.

Recovery of pituitary-gonadal function usually occurs within 8 weeks of discontinuing treatment.

There may be an exacerbation of symptoms of pain and increase in nodular mass and pressure during the first few weeks of treatment.
In the initial treatment with buserelin, ovarian cysts may develop.

Each stimulation must be monitored carefully to permit early identification of affected patients. If necessary, administration of human chorionic gonadotrophin (hGC) must be foregone.

For the preparation for Ovulation induction: Before treatment is started, it is recommended that a pregnancy test be performed. In in-vitro fertilisation, induction of ovulation must be performed under close medical supervision. Risks specific to IVF/ET and related assisted reproduction procedures such as increase in miscarriages, ectopic and multiple pregnancies are unaltered under adjunctive use of buserelin. In addition, follicle recruitment may be increased especially in patients with polycystic ovary disease PCOD.

The combination of gonadotrophins with buserelin carries a higher risk of development of ovarian hyperstimulation syndrome (OHSS) than the use of gonadotrophins alone. Each stimulation cycle must be monitored carefully to permit early identification of affected patients. If necessary, administration of human chrionic gonadotrophin (hCG) must be foregone.

In patients with polycystic ovarian syndrome, caution is recommended, because there is an increased tendency towards ovarian hyperstimulation syndrome when combined with gonadotropines.

Possible clinical signs of ovarian hyperstimulation syndrome (OHSS) include: abdominal pain, feeling of abdominal tension, increased abdominal girth, occurrence of ovarian cysts, nausea, vomiting, as well as massive enlargement of the ovaries, dyspnoea, diarrhoea, oliguria, haemoconcentration, hypercoagulability. Pedicle tension or rupture of the ovary may lead to an acute abdomen.

Severe thromboembolic events may also occur. Fatal outcome is possible.

Ovarian cysts have been observed in the initial phase of buserelin treatment. No impact on the stimulation cycle has been reported so far.

4.5 Interaction with other medicinal products and other forms of interaction

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Suprecur 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).

If nasal decongestant are being used concurrently they should be administered at least 30 minutes after the buserelin.

During treatment with buserelin, the effect of antidiabetic agents may be attenuated (see also under section 4.8 Undesirable effects).

In concomitant treatment with sexual hormones ("add back"), the dosage is to be selected so as to ensure that the overall therapeutic effect is not affected.

4.6 Fertility, pregnancy and lactation

Suprefact must not be administered in case of pregnancy (see also under section 4.3 Contraindications)

Buserelin passes into breast milk in small amounts. Although negative effects on the infant have not been observed, it is recommended that breast-feeding be avoided during treatment with Suprefact in order to prevent the infant from ingesting small quantities of buserelin with breast-milk.

4.7 Effects on ability to drive and use machines

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).

4.8 Undesirable effects

Buserelin treatment may also lead to:

- Skin and subcutaneous tissue disorders: changes in scalp and body hair (increase/decrease)
- Vascular disorders: deterioration in blood pressure levels in patients with hypertension.
- Immune systems disorders: hypersensitivity reactions. These may manifest as, e.g. reddening of the skin, itching, skin rashes (including urticaria), and allergic asthma with dyspnoea, as well as, in isolated cases, lead to anaphylactic/anphylactoid shock.
- Psychiatric disorders: nervousness, emotional instability, feelings of anxiety. Mood changes and depression (long term use:common, short term use:uncommon, as observed with GnRH agonists). Depression may develop or existing depression may worsen.
- Metabolic and nutrition disorders: increased thirst, changes in appetite, reduction in glucose tolerance. This may, in diabetic patients, lead to deterioration of metabolic control.
- Neoplasm benign, malignant and unspecified (including cysts and polyps): Very rare cases of pituitary adenomas were reported during treatment with LHRH agoinists, including buserelin.
- General disorders and administration site reactions: tiredness
- Investigations: changes in blood lipids, increase in serum levels of liver enzymes (e.g. transaminases), increase in bilirubin, weight changes (increase or decrease)
- Blood and lymphatic system disorders: thrombopenia and leucopenia
- Cardiac disorders: palpitations. Frequency unknown/rare/uncommon*: QT prolongation (see sections 4.4 and 4.5)
  *frequency as derived from clinical trials/safety studies, if no data is available frequency should be labelled as "unknown".
- Nervous system disorders: headache (in women, in rare cases migraine like), nervousness, sleep disturbances, fatigue (asthenia), drowsiness, disturbances of memory and concentration, emotional instability, feelings of anxiety, dizziness. In rare cases depression may develop or existing depression may worsen.
- Ear and labyrinth disorders: tinnitus, hearing disorders
- Eye disorders: impaired vision (e.g. blurred vision), feeling of pressure behind the eyes.

- Gastrointestinal disorders: nausea, vomiting, diarrhoea, constipation, changes in appetite.

- Musculoskeletal and connective tissue disorders: Muscoskeletal discomfort and pain (including shoulder pain and stiffness in women).
  The use of LHRH-agonists may be associated with decrease in 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.

Nasal administration may irritate the mucosa in the nasopharynx. This may lead to nosebleeds and hoarseness as well as to disturbances of smell and taste.

In-vitro fertilization/embryo transfer programs and similar assisted reproduction procedures carry inherent risks, e.g. increased occurrence of ectopic pregnancies, miscarriages or multiple pregnancies; this also applies where buserelin is used as adjunctive therapy. The fact that follicle recruitment may be increased under buserelin treatment (especially in the case of polycystic ovaries) may, however, in some patients also represent a desirable effect.

Combined use of buserelin with gonadotropins may carry a higher risk of ovarian hyperstimulation syndrome (OHSS) than the use of gonadotropins alone (see also under 4.4).

Degeneration of uterine fibroids in women with uterine fibroids

Nasal administration may irritate the mucosa in the nasopharynx. This may lead to nosebleeds and hoarseness as well as to disturbances of smell and taste.

Treatment with buserelin inhibits oestrogen production. In addition to the intended effects this may lead also to adverse effects (dose-dependent) ie. where buserelin for preparation for ovulation induction is used at low dosage, these effects occur less frequently and are less pronounced than in the treatment of endometrosis.

As manifestation of inhibited oestrogen production, in most cases uterine bleeding occurs during the first week of treatment. Uterine bleeding may also occur in the further course of treatment.

As additional manifestation of inhibited oestrogen production, menopausal-like symptoms may also occur, such as hot flushes, increased sweating, vaginal dryness, dyspareunia, decreased libido, and after several months treatment, a decrease in bone mass. See under Section 4.4 Special Warnings and Precautions for use.

Further adverse events not directly attributable to hormone deprivation: increase or decrease in breast size with breast tenderness, splitting nails, acne, dry skin, and occasionally vaginal discharge and oedema of the face and extremities (occasional, arm and legs).

In the initial phase of treatment with buserelin ovarian cysts may develop. For preparation of ovulation induction, however, no negative effect on the course of stimulation has been reported so far.
In addition, vomiting, lactation, stomach ache, lower abdominal pain, or paraesthesia (especially in the arms or legs) may occur as may dryness of the eye (may lead to eye irritation in wearers of contact lenses).

Very rare cases of pituitary adenomas were reported during treatment with LH RH agonists, including buserelin.

In-vitro fertilisation/embryo transfer programs and similar assisted reproduction procedures carry inherent risks e.g. increased occurance of ectopic pregnancies, miscarriages or multiple pregnancies; this also applies where buserelin is used as adjunctive therapy. The fact that follicle recruitment may be increased under buserelin treatment (especially in the case of polycystic ovaries) may, however, in some patients also represent a desirable effect.

Combined use of buserelin with gondatrophins may carry a higher risk of ovarian hyperstimulation syndrome (OHSS) than the use of gondatrophins alone. See also under section 4.4 Special Warnings and Precautions for Use.

Degeneration of uterine fibroids in women with uterine fibroids

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 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

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, as well as local reactions at the injection site such as pain, haemorrhage and induration. Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Buserelin is an analogue of the natural gonadotrophin-releasing hormone (gonadorelin; (GnRH)) with enhanced biological activity.

After repeated administration of buserelin, the secretion of gonadotrophins and gonadal steroids is significantly inhibited.

The pharmacological effect is attributable to the down-regulation of pituitary LH-RH receptors.

In male individuals the elimination of gonadotrophin release results in a lasting reduction in the synthesis and secretion of testosterone.

In female individuals the elimination of pulsatile gonadotrophin release reliably inhibits the secretion of oestrogen.

The suppressive effect of buserelin on the secretion of gonadal steroids depends on the daily dose, the frequency of application and the duration of treatment.

Even when the serum level of buserelin is below the detection limit, gonadotrophin release is preserved because of sustained binding to the receptors of the anterior lobe of the pituitary gland (approx. 3 hours).

While gonadotrophin release is inhibited during long-term treatment with buserelin, the secretion of the other pituitary hormones (growth hormone, prolactin, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH)) is not directly influenced. However, oestrogen deficiency may lead to decreased secretion of growth hormone and prolactin. The secretion of adrenal steroids remains unchanged.

In terms of the complete inhibition of testicular testosterone synthesis, buserelin is equally effective as orchiectomy in the treatment of prostatic carcinoma. Compared with orchiectomy, buserelin offers the advantage of reversibility and reduced psychological stress for the patient.

5.2 Pharmacokinetic properties

Buserelin is water-soluble; when administered by subcutaneous injection it is reliably absorbed.

If administered correctly by the nasal route, it is absorbed via the nasal mucosa in such a way that sufficiently high plasma levels are guaranteed. The biological activity of buserelin was not impaired even after the induction of histamine rhinitis in test subjects.

The nasal absorption of buserelin from buserelin nasal solution is 1 to 3%. After subcutaneous injection of 200micrograms buserelin is 70% bioavailable; in contrast, after oral administration, buserelin is ineffective.

Buserelin accumulates preferentially in the liver and kidneys as well as in the anterior pituitary lobe, the biological target organ.

The elimination half-life is approx. 50 to 80 minutes following intravenous administration, 80 to 120 minutes after subcutaneous administration and approx. 1 to 2 hours after intranasal administration.

Buserelin circulates in serum predominantly in intact active form. Protein binding is approx. 15%. Buserelin and inactive buserelin metabolites are excreted via the renal and biliary route. The serum concentration and the excretion of buserelin in the urine show the same time profile. In man approx. 50% of buserelin excreted in the urine is intact.

Buserelin is metabolised by peptidases (pyroglutamyl peptidase and chymotrypsin-like endopeptidases) in the liver and kidneys as well as in the gastrointestinal tract and by this means inactivated. In the pituitary gland, receptor-bound buserelin is inactivated by membrane-located enzymes.

A small proportion of the dose of buserelin is secreted into the breast milk. According to present clinical experience these amounts have no hormonal effect on the infant.

5.3 Preclinical safety data

None of clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Sodium chloride
Sodium dihydrogen phosphate
Benzyl alcohol
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

Unopened: 2 years.
Opened: 7 days.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.
Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Box of 1 x 5.5 ml multidose vial. Each vial consists of clear, colourless, Type I (Ph. Eur.) glass with a grey chlorobutyl rubber and an aluminium/polypropylene combination seal. Pack size: 2 individual cardboard boxes are wrapped together in a clear plastic outer.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Ltd. T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/074/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 August 1986

Date of last renewal: 16 August 2009

10 DATE OF REVISION OF THE TEXT

August 2015