# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Suprecur 150 micrograms/ metered dose Nasal Spray, solution.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (100mg) contains 150 micrograms buserelin, as buserelin acetate.
150 micrograms buserelin is equivalent to 157.5 micrograms buserelin acetate.

Excipients: Suprecur nasal spray contains 10 micrograms of Benzalkonium chloride per metered dose.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Nasal Spray, Solution
Clear, colourless to pale yellow solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

The treatment of endometriosis, unless the disease primarily requires surgical treatment.

Pituitary desensitisation in preparation for ovulation induction, as an adjunct to gonadotropin administration.

### 4.2 Posology and method of administration

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

*Adult females (over the age of 18 years)*

*Endometriosis:* Regardless of body weight, the usual dose is 300 micrograms, thrice daily (given as a spray to each nostril). The product may be used before or after meals or at other times, provided that uniform intervals are maintained between doses.

The usual duration of treatment is 6 months since there is no experience of longer use, only limited experience of retreatment. It is recommende that the duration of treatment does not exceed 9 months.

In the case of transfer of patients from danazol to Suprecur, it might be preferable on theoretical grounds to consider an overlap of 2 – 3 days.

*For adjunctive use in ovulation induction:* The total daily intranasal dose for this indication is 600 micrograms buserelin, given in four divided dosages of 150 micrograms (one spray in one nostril) spread over the waking hours. Treatment should start in the early follicular phase (day 1) or, provided the existence of an early pregnancy has been excluded in the mid-luteal phase (day 21). It should continue at least until down-regulation is achieved e.g. serum oestradiol <50 ng/l and serum progesterone <1 microgram/l. This will usually take about 2-3 weeks. In some patients, dosages up to 4 x 300 micrograms may be required to achieve these levels. When down-regulation is achieved, stimulation with gonadotropin is commenced while the dosage of buserelin is maintained. At the appropriate stage of follicular development, gonadotropin 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.

If used correctly, reliable absorption of the active ingredient takes place via nasal mucous membranes. The drug is absorbed even if the patient has a cold; however, in such cases the nose should be blown thoroughly before administration.

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

*Children:* Suprecur is not suitable for use in children.

*Elderly:* Suprecur is not suitable for use in post-menopausal women.

## 4.3 Contraindications

Suprecur must not be administered in patients with hypersensitivity to buserelin or, if applicable, to any of the excipients.

Suprecur must not be administered in case of pregnancy (see also under section 4.6 Pregnancy and Lactation), undiagnosed vaginal bleeding, hormone dependent neoplasms.
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

Suprecur Nasal Spray must not be administered in case of pregnancy(see also under section 4.3 Contraindications).

There is no indication for use of Suprecur during pregnancy because of its suppressive effect on the pituitary hypothalamic-gonadal axis. It is recommended to exclude pregnancy before starting treatment and in ovulation induction regimes to stop Suprecur on the first day of Hcg treatment.

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 Suprecur Nasal Spray 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 those 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, oedema of the lower extremities and mastodynia. Treatment should be symptomatic.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC Code: L02AE01

Buserelin is a synthetic peptide. It is a superactive analogue of natural gonadotrophin releasing hormone (gonadorelin, LHRH or GnRH). After an initial stimulation of gonadotrophin release, it down-regulates the hypothalamic-pituitary-gonadal axis.

## 5.2 Pharmacokinetic properties

Metabolic inactivation by peptidase occurs in the liver and kidney. The drug is also inactivated by pituitary membrane enzymes.

## 5.3 Preclinical safety data

None of clinical relevance.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium chloride
Sodium citrate
Citric acid monohydrate
Benzalkonium chloride
Water for injections

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

Unopened: 3 years.
Opened: 5 weeks.

## 6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.

## 6.5 Nature and contents of container

Moulded brown glass narrow-necked bottle with a white HDPE screw cap and an ethylene vinyl acetate copolymer or low density polyethylene plastic stopper and a metered dose nebuliser.

Each pack of Suprecur nasal spray contains 1 bottle with 10 g of solution and also contains a metered dose nebuliser.

## 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

How to use the spray bottle:

1. Remove spray cap from bottle.
2. Remove metered dose nebuliser from transparent plastic container and take off both protective caps.
3. Screw nebuliser on to bottle.
4. Before first application only, pump 5-8 times, holding bottle vertical, until the solution has filled the system and a uniform spray is emitted. The preliminary pumping is for the purpose of filling the system and testing the spray.
   It must not be repeated after the first use, in order to avoid wasting the contents.
5. Keeping the bottle vertical and bending head over it slightly, spray solution into nose. If necessary the nose should be cleaned before applying the solution.
6. After use leave nebuliser on bottle. After replacing protective cap, spray bottle is best stored in its transparent container in an upright position.

# 7 MARKETING AUTHORISATION HOLDER

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

# 8 MARKETING AUTHORISATION NUMBER

PA0540/073/002

# 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 February 1991

Date of last renewal: 16 August 2009

## 10 DATE OF REVISION OF THE TEXT

January 2017