SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Suprecur Injection 1 mg/ml solution for injection
Buserelin 1 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml Buserelin Injection contains 1.05 mg buserelin acetate as active ingredient, equivalent to 1.00 mg/ml buserelin.

Excipients with known effect: sodium, benzyl alcohol.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.

Clear, colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pituitary desensitisation in preparation for ovulation induction regimens using gonadotrophins.

4.2 Posology and method of administration

Posology

The total daily dose is usually in the range 200 – 500 microgram (µg).
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 < 180 pmol/l and serum progesterone < 3 nmol/l. This will usually take about 1 - 3 weeks.
Doses may have to be adjusted for individuals. Occasionally, patients may require up to 500 µg twice daily in order to achieve down-regulation.
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 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.

Method of administration
The daily dosage is given as a single injection by the subcutaneous route.

4.3 Contraindications

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

Buserelin should not be used in cases of undiagnosed vaginal bleeding.

It must not be used during pregnancy or lactation (see section 4.6 Pregnancy and lactation).

4.4 Special warnings and precautions for use

Buserelin Injection is for subcutaneous administration ONLY.

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 known to suffer from depression should be carefully monitored and treated if necessary during treatment with Buserelin Injection (risk of recurrence or worsening of depression).

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

QT Prolongation
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 Buserelin Injection.

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).

Before treatment is started, it is recommended that a pregnancy test be performed.

In in-vitro fertilization, induction of ovulation must be performed under close medical supervision. Therefore, treatment with Buserelin Injection should be initiated only under the supervision of a specialist with experience of the indication.

Whenever the treatment is self-administered, it is strongly recommended that initial doses should be administered under close medical supervision due to the possibility of hypersensitivity reactions. Patients should cease injections and seek medical attention should any adverse event occur which may represent an allergic reaction.

Induction of ovulation should be carried out 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. However, follicle recruitment may be increased especially in patients with polycystic ovarian disorder (PCOD).

Combined use of buserelin with gonadotropins may bear a higher risk of ovarian hyperstimulation syndrome (OHSS) than the use of gonadotropins alone.

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

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 torsion or rupture of the ovary may lead to an acute abdomen. Severe thromboembolic events may also occur. Fatal outcome is possible.

The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS. hCG should be withheld if necessary.

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

Anti-doping information

The use of the medicinal product may lead to positive results in doping tests. In addition, misuse as a doping agent may endanger health.

Warnings on excipients

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

This medicine contains 2 - 5 mg benzyl alcohol in each dosage unit (depending on the applied dose) which is equivalent to 10 mg/ml solution.
Benzyl alcohol may cause allergic reactions.
Take care with pregnant or breast□feeding women. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).

High volume should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicinal products and other forms of interaction

During treatment with Buserelin Injection, the effect of antidiabetic agents may be attenuated.

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.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Buserelin Injection 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 Pregnancy and lactation

Pregnancy must be excluded before starting buserelin and the medication should be stopped on the day of administration of hCG.

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 Buserelin Injection 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 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

The following CIOMS frequency rating is used: *Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1000); very rare (<1/10 000), not known (cannot be estimated from the available data).*

After administration of the injection, pain or local reaction at the injection site is possible. Hypersensitivity reactions may also occur. These may become manifest for example as reddening of the skin, itching, skin rashes (including urticaria) and allergic asthma with dyspnoea as well as, in isolated cases, anaphylactic/anaphylactoid shock.

Treatment with buserelin inhibits oestrogen production. As evidence of the biological response to hormone deprivation, patients may experience menopausal-like symptoms and withdrawal bleeding, which are directly related to the pharmacological action of the drug. Symptoms such as hot flushes, increased sweating, dry vagina, dyspareunia and loss of libido generally occur some weeks after starting treatment and may be severe in

some patients. Withdrawal bleeding may occur during the first few weeks of treatment. Breakthrough bleeding may occur during continuing treatment. **After several months' treatment, a decrease in bone mass may occur.**

Changes in bone density: a decrease in bone mineral, the magnitude of which relates to the duration of therapy, occurs during treatment with buserelin alone. The evidence available indicates that six months treatment is associated with a decrease in bone mineral density of the spine of 3.5 %. These changes are similar to those seen with other agonists. Increased levels of serum alkaline phosphatase may occur.

Other adverse effects may include:

Neoplasms benign and malignant – Very rare cases of pituitary adenomas were reported during treatment with LH-RH agonists, including buserelin.

Blood disorders – Very rare cases of thrombocytopenia or leukopenia.

Metabolism and nutrition disorders – Frequent increase or decrease in weight Occasional changes in appetite and increased thirst. Rarely increase or decrease in blood lipid levels. Very rarely, reduction in glucose tolerance which may lead to the worsening of metabolic control in diabetics.

Psychiatric disorders – Frequent nervousness, emotional instability. Occasional anxiety, depression or worsening of existing depression.
Mood changes, depression, frequency: Long term use: Common
Short term use: uncommon

Nervous system disorders – Dizziness, headache (in women in rare cases migraine-like), sleep disturbances, tiredness, drowsiness. Occasional paraesthesia (especially in the arms and legs), disturbances of memory and concentration.

Eye disorders – Occasional dry eyes (possibly leading to eye irritations in people who wear contact lenses), impaired vision (e.g. blurred vision), feeling of pressure behind the eyes.

Ear and labyrinth disorders – Rare cases of tinnitus, hearing disorders found.

Cardiac disorders – Frequent palpitations.
Frequency unknown: QT prolongation (see sections 4.4 and 4.5)

Vascular disorders – Occasional oedema (of face and extremities) and hot flushes. Very rare cases of a deterioration of blood pressure levels in patients with hypertension.

Gastrointestinal disorders – Frequent lower abdominal pain, stomach ache, nausea, vomiting, diarrhoea, constipation.

Hepato-biliary disorders – Occasional increase in serum liver enzyme levels (e.g. transaminases), increase in serum bilirubin.

Skin and subcutaneous tissue disorders – Frequent dry skin, acne, increase or decrease in scalp hair (alopecia, hirsutism). Occasional increase or decrease in body hair, splitting nails.

Musculoskeletal and bone disorders – Frequent musculoskeletal discomfort and pain (including shoulder pain/stiffness). 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 – Frequent Vaginal discharge, increase or decrease in breast size, breast tenderness. Occasional lactation.

In the initial phase of treatment with buserelin, ovarian cysts may develop (see also section 4.4). For preparation of ovulation induction, however, no negative effect on the course of stimulation has been reported so far.

In-vitro fertilization/embryo transfer programmes 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 bear a higher risk of ovarian hyperstimulation syndrome (OHSS) than the use of gonadotropins alone (see section 4.4).

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 to local reactions at the injection site such as pain, haemorrhage and induration (see section 4.8). Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents - endocrine therapy - hormones and related agents - gonadotropin releasing hormone analogues - buserelin, 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 (HPO) axis such that a decrease in ovarian steroid secretion into the post-menopausal range occurs. The time taken to achieve these levels varies between individuals and with the regimen of administration, so that close monitoring of circulating levels of oestradiol and progesterone should be performed during treatment. This effect provides an appropriate setting for the administration of follicle-stimulating therapy and reduces the incidence of premature ovulation by inhibition of surges in LH.

5.2 Pharmacokinetic properties

The bioavailability of buserelin after subcutaneous injection is 100 %. C_{max} occurs at about 1 hour post-injection. The half-life after injection is about 80 minutes.

Buserelin accumulates preferentially in the liver, kidneys and in the anterior pituitary lobe, the biological target organ. Buserelin circulates in serum predominantly in the intact, active form. Protein binding is about 15 %.

Buserelin is inactivated by peptidases (pyrogutamyl peptidase and chymotrypsin-like endopeptidases) in the liver and kidneys. In the pituitary gland, receptor-bound buserelin is inactivated by membrane-located enzymes. Buserelin and inactive buserelin metabolites are excreted via the renal and the biliary route.

5.3 Preclinical safety data

No signs of toxicity or histopathological changes were detected in long-term pharmacology and toxicology studies with buserelin in rats, dogs, and monkeys; the endocrine effects observed were restricted to the gonads. Pituitary adenoma occurred during long-term treatment in rats, this phenomenon has not been found in dogs and monkeys. There are no indications of a mutagenic or carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride Ph. Eur.
Sodium dihydrogen phosphate BP.
Sodium hydroxide BP.
Benzyl alcohol BP.
Water for injection Ph. Eur.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years (see section 6.6).

Once opened use within 15 days.

6.4 Special precautions for storage

Do not store above 25 ^{o}C. Do not freeze. Keep the vials in the outer carton in order to protect from light.

6.5 Nature and contents of container

Box of 2 x 5.5 ml multidose vials.

6.6 Special precautions for disposal and other handling

Each vial contains enough material for 10 doses. After finishing the course of treatment the vial should be disposed of and a new vial started for the next treatment. Do not use if the contents of the vial are cloudy or discoloured. Patients should be instructed on the correct handling of the vial (aseptic technique) by a doctor or nurse.

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

7 MARKETING AUTHORISATION HOLDER

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SG12 9PY
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8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0051

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

28/09/2022