

Data Sheet

SUPREFACT

Buserelin acetate

Presentation

Suprefact Injectable

Injection solution in 5.5 mL vials, each 1 mL containing 1.05 mg buserelin acetate as the active substance, equivalent to 1 mg buserelin, in aqueous solution, and benzyl alcohol as preservative.

Uses

Actions:

Buserelin is a potent analogue of the hypothalamic peptide LHRH. It competes with its parent molecule for binding sites on the anterior pituitary cells secreting LH and FSH. Initial effects are to increase secretion of the gonadotrophins, but provided that sufficient doses are used with sufficient regularity, the activity of the hypothalamic-pituitary-axis is down-regulated.

In female individuals the elimination of pulsatile gonadotrophin release reliably inhibits the secretion of oestrogen. After treatment is stopped the ovulatory cycle is resumed in most patients within 6 to 8 weeks. The first menstrual bleed occurs after about 10 weeks.

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

Pharmacokinetics

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

After subcutaneous injection of 200 mcg, 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 approximately 50-80 minutes following intravenous administration and 80-120 minutes following subcutaneous administration.

Buserelin circulates in the serum, predominantly in intact, active form. Protein binding is approximately 15%. Buserelin and inactive buserelin metabolites are excreted via the renal and the biliary route. The serum concentration and the excretion of buserelin in the urine show the same time profile. In women given intravenous buserelin, 20 to 30% of the dose was recovered from the urine, 50% of which was the intact substance. The main metabolite was the 5-9 fragment.

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-localised enzymes.

Indications

For the treatment of endometriosis not primarily requiring surgical treatment.

Pituitary desensitisation in preparation for ovulation induction regimens using gonadotrophins.

For the treatment of advanced hormone-dependant prostatic carcinoma; however, not after bilateral orchiectomy (no further reduction of testosterone level by buserelin to be expected).

Dosage and Administration

Before commencing therapy, the possibility of pregnancy should be excluded.

For Endometriosis :

200 mcg buserelin by S.C. injection increasing to 500 mcg daily, depending upon symptomatic response.

Treatment should be started on the first or second day of the menstrual period in order to exclude, as far as possible, the existence of pregnancy. Treatment is usually given for 6 months and should not exceed 9 months.

The inception of buserelin treatment may cause ovulation and contraceptive measures should be in place.

For Adjunctive use in Ovulation Induction

600 mcg buserelin by S.C. injection as a divided dose 3 times daily.

Treatment should start in the early follicular phase (day 1) or, provided the existence of any early pregnancy has been excluded, in the midluteal phase (day 21). It should continue at least until down-regulation is achieved (ie. serum oestradiol < 50 ng/l and serum progesterone < 1 mcg/l). This will usually take about 2-3 weeks with nasal spray administration, and is less with parenteral use.

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 hCG is given to induce ovulation.

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

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

For Treatment of Prostatic Carcinoma

Regardless of body weight, the daily dose is 1.5 mg buserelin. The daily dose is to be administered in the form of a S.C. injection as three single doses of 0.5 mL buserelin, each spread throughout the day at approximately equal intervals.

From the 8th day of treatment onwards, treatment is continued using buserelin nasal spray.

Contraindications

Hypersensitivity to buserelin acetate, LHRH or benzyl alcohol.

For Endometriosis and Adjunctive use in Ovulation Induction

Pregnancy, lactation, undiagnosed vaginal bleeding, hormone dependent neoplasms.

For Treatment of Prostatic Carcinoma

Should not be used if tumour is found to be insensitive to hormone manipulation or after surgical removal of the testes.

Warnings and Precautions

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

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

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).

For Endometriosis and Adjunctive use in Ovulation Induction

Combined use of buserelin with gonadotrophins may bear a higher risk of ovarian hyperstimulation syndrome (OHSS) than the use of gonadotrophins alone. The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS. hCG should be withheld if necessary.

A decrease in bone mineral, the magnitude of which relates to the duration of therapy, occurs during treatment with buserelin. The evidence available for intra nasal spray administration 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.

For Treatment of Prostatic Carcinoma

Monitoring of the chemical effect of buserelin is carried out by the methods generally used in prostatic carcinoma. Initially serum testosterone levels rise and a clinical effect will not be seen until levels start to fall within the therapeutic (castration) range. Disease flare (temporary deterioration of patient's condition) has been reported at the beginning of treatment.

The incidence is variable, but of the order of 10%. Symptoms are usually confined to transient increase in pain but the exact nature depends on the site of the lesions. Neurological sequelae have been reported where secondary deposits impinge on the spinal cord or CNS. Disease flare is prevented by the prophylactic use of an antiandrogen, eg. cyproterone acetate, 300 mg daily. It is recommended that treatment should be started at least 3 days before the first dose of buserelin and continued for at least 3 weeks after commencement of buserelin therapy.

Once testosterone levels have started to fall below their baseline concentration clinical improvement should start to become apparent. If testosterone levels do not reach the therapeutic range within 4 weeks (6 weeks at the latest) the dose schedule should be checked to be sure it is followed exactly. It is unlikely that a patient who is taking the full dose will not show a suppression of testosterone to the therapeutic range. If this is the case, alternative therapy should be considered.

A proportion of patients will have tumours which are not sensitive to hormone manipulation. Absence of clinical improvement in the face of adequate testosterone suppression is diagnostic of this condition, which will not benefit from further therapy with buserelin.

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.

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

Use During Pregnancy and Lactation

There is no indication for use of buserelin 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 regimens to stop buserelin treatment on the first day of hCG treatment.

It is unlikely that pregnancy will occur in the later stages if the recommended doses are taken regularly. However, if the treatment is interrupted for even a few days, ovulation may occur and the patient may become pregnant. In this event buserelin should be discontinued immediately.

Buserelin is excreted in small quantities in mother's milk and therefore should not be prescribed to lactating mothers. According to present clinical evidence these amounts have no hormonal effect on the infant.

Adverse Effects

For All Indications

Buserelin treatment may lead to:

Investigations: changes in blood lipids, increase in serum levels of liver enzymes (eg. transaminases) increase in bilirubin, weight changes (increase or decrease).

Cardiac disorders: palpitations

Blood and lymphatic system disorders: thrombopenia and leucopenia.

Nervous system disorders: headache (in women in rare cases migraine-like), sleep disturbances, drowsiness, disturbances of memory and concentration, dizziness.

Eye disorders: impaired vision (eg. blurred vision), feeling of pressure behind the eyes.

Ear and labyrinth disorders: tinnitus, hearing disorders.

Gastrointestinal disorders: nausea, vomiting, diarrhea, constipation.

Skin and subcutaneous tissue disorders: changes in scalp and body hair (increase or decrease).

Musculoskeletal and connective tissue disorders: musculoskeletal discomfort and pain (including shoulder pain/stiffness in women). 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 duration of therapy.

Metabolic and nutrition disorders: increased thirst, changes in appetite, reduction in glucose tolerance. This may, in diabetic patients, lead to a 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 agonists including buserelin.

Vascular disorders: deterioration in blood pressure levels in patients with hypertension.

General disorders and administration site reactions: tiredness.

Immune system disorders: hypersensitivity reactions. These may manifest as reddening of the skin, itching, skin rashes (including urticaria) and allergic asthma with dyspnoea as well as, in isolated cases, lead to anaphylactic/anaphylactoid shock.

Psychiatric disorders: nervousness, emotional instability, feelings of anxiety. In rare cases, depression may develop or existing depression may worsen.

Pain or local reactions at the injection site are possible.

For Endometriosis, and Adjunctive use in Ovulation Induction

As evidence of the biological response to hormone deprivation many patients will experience menopausal-like symptoms and withdrawal bleeding, which are directly related to the pharmacological action of the drug. Menopausal-like symptoms, such as hot flushes, increased sweating, dyspareunia, dry vagina and loss of libido 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 the further course of the treatment. Bone loss may occur during treatment (see under Warnings) and (Dosage and Administration).

Further adverse events not clearly attributable to hormone deprivation include: breast tenderness and changes in breast size (increase/decrease), splitting nails, acne, dry skin, vaginal discharge, oedema on the face and extremities.

In addition, lactation, stomach-ache, lower abdominal pain, paraesthesia (especially in the arms or legs) may occur, as may dryness of the eyes.

In the initial phase of treatment with buserelin, ovarian cysts may develop.

In-vitro fertilisation/embryo transfer programs and similar assisted reproduction procedures carry inherent risks eg. increased occurrence of ectopic pregnancies, miscarriages or multiple pregnancies; this also applies where buserelin is used as adjunctive therapy.

Combined use of buserelin with gonadotrophins may carry a higher risk of ovarian hyperstimulation syndrome (OHSS) than use of gonadotrophins alone.

For Treatment of Prostatic Carcinoma

At the beginning of treatment, a transient rise in the 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 neurological deficit due to tumour compression eg. muscle weakness in the legs, impaired micturition, hydronephrosis or lymphostasis or thrombosis with pulmonary embolism.

Additionally, hot flushes, loss of potency or libido (in most cases the result of hormone deprivation), and atrophy of the testes, usually painless gynaecomastia as well as mild oedemas of the ankles and lower legs may occur.

Effects on Ability to Drive and Operate Machinery

Certain adverse effects (eg, dizziness) may impair the patients ability to concentrate and react, and, therefore, constitute a risk in situations where these abilities are of special importance (eg, operating a vehicle or machinery).

Interactions

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

For Endometriosis and Adjunctive use in Ovulation Induction

In concomitant treatment with sexual hormones, the dosage is to be selected so that the overall therapeutic effect is not affected.

Overdosage

Overdosage may lead to signs and symptoms such as asthenia, headache, nervousness, hot flushes, dizziness, 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.

Treatment for overdosage is symptomatic and supportive.

Pharmaceutical Precautions

Store at room temperature.

Medicine Classification

Prescription Medicine.

Package Quantities

Injection: Packs of 2 x 5.5 mL vials.

Further Information

Nil.

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