# DATA SHEET

# 1 SUPREFACT® 1 MG/ML SOLUTION FOR INJECTION

Suprefact 1 mg/mL solution for injection.

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 1.05 mg of buserelin acetate as the active substance, equivalent to 1 mg buserelin, in aqueous solution, and benzyl alcohol as preservative.

For the full list of excipients, see section 6.1 List of excipients.

# 3 PHARMACEUTICAL FORM

Solution for injection.

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC 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).

## 4.2 DOSE AND METHOD OF ADMINISTRATION

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

### Dose

#### *For Endometriosis*

200 micrograms buserelin by subcutaneous (S.C) injection increasing to 500 micrograms 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 micrograms 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 microgram/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 human chorionic gonadotropin (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.

***Paediatric population***

The safety and efficacy of buserelin acetate in children aged under 18 years has not been established.

## 4.3 CONTRAINDICATIONS

Hypersensitivity to buserelin acetate, luteinising-hormone-releasing hormone (LHRH), benzyl alcohol or any of the excipients listed in section 6.1.

Because of the content of benzyl alcohol, Suprefact must not be given to newborns or premature neonates.

### 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.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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).

The administration of medications containing benzyl alcohol to newborns or premature neonates has been associated with a fatal “Gasping Syndrome” (symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardio-vascular collapse). As benzyl alcohol may cross the placenta, solution for injection should be used with caution in pregnancy.

### 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 physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating buserelin. In case of QT prolongation, buserelin treatment should be discontinued (see sections 4.5 and 4.8).

### 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.

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.

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 of disease flare 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 LHRH 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, LHRH agonist therapy may increase the risk of anaemia. Patients should be evaluated for this risk and managed accordingly.

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

### For 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-existing pregnancy at the beginning of therapy, it is recommended that treatment be started on the first or second day of menstruation. If there is any doubt, a pregnancy test is recommended.

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 and a physician must be informed.

Repeated courses of treatment must only be administered after a 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.

### For 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.

## 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of buserelin 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. In case of combination with such medicinal products, the QT interval should be closely monitored (see section 4.4).

### 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.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Pregnancy

Buserelin must not be administered in case of pregnancy (see section 4.3).

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.

As benzyl alcohol may cross the placenta, solution for injection should be used with caution in pregnancy (see section 4.4).

### Breast-feeding

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

### Fertility

Suprefact is indicated for pituitary desensitisation in preparation for ovulation induction regimens using gonadotrophins (section 4.1). See sections 4.2 and 5.1 for further information.

## 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 (eg, 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). Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

## 4.8 UNDESIRABLE 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.

### Post-Marketing Experience

Cardiac disorders: Post-marketing experience with frequency not known: Androgen deprivation therapy treatment may lead to QT prolongation (see sections 4.4 and 4.5).

### For Endometriosis and Adjunctive use in Ovulation Induction

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

As manifestation of inhibited oestrogen production, in most cases uterine bleeding ("period") occurs during the first weeks of treatment. Uterine bleeding may also occasionally occur in the further course of treatment.

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 sections 4.4 and 4.2).

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 e.g. 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 e.g. muscle weakness in the legs, impaired micturition, hydronephrosis or lymphostasis or thrombosis with pulmonary embolism.

Such reactions can be largely avoided when an anti-androgen is given concomitantly in the initial phase of buserelin treatment.

However, even with concomitant anti-androgen therapy, a mild but transient increase in tumour pain as well as a deterioration in general well-being may develop in some patients.

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.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

### 4.9 OVERDOSE

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Gonadotropin releasing hormone analogues, ATC code: L02AE01.

### Mechanism of Action

Buserelin is a potent analogue of the hypothalamic peptide LHRH. LHRH is also known as gonadotrophin-releasing hormone (GnRH). It competes with its parent molecule for binding sites on the anterior pituitary cells secreting luteinising-hormone (LH) and follicle-stimulating hormone (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.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

Buserelin is water soluble; when administered by subcutaneous (S.C.) injection it is reliably absorbed.

After subcutaneous injection of 200 microgram , buserelin is 70% bioavailable; in contrast, after oral administration, buserelin is ineffective.

### Distribution

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

Buserelin circulates in the serum, predominantly in intact, active form. Protein binding is approximately 15%.

### Biotransformation

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.

### Elimination

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.

The elimination half-life is approximately 50-80 minutes following intravenous administration and 80-120 minutes following subcutaneous administration.

## 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

Benzyl alcohol

Monobasic sodium phosphate dihydrate

Sodium chloride

Sodium hydroxide

Water for injections

## 6.2 INCOMPATIBILITIES

Not applicable.

## 6.3 SHELF LIFE

2 years

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25°C protect from light.

## 6.5 NATURE AND CONTENTS OF CONTAINER

Packs of 2 x 5.5 mL vials.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL.

No special requirements for disposal.

# 7 MEDICINE SCHEDULE

Prescription

# 8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street, Ellerslie,

Auckland, New Zealand
New Zealand Free Call: 0800 283 684
Email: medinfo.australia@sanofi.com

# 9 DATE OF FIRST APPROVAL

15 February 1990

# 10 DATE OF REVISION OF THE TEXT

19 September 2018

### Summary of changes

| Section changed | Summary of new information |
|---|---|
| All | Align with the Medsafe data sheet format including minor additions of text to meet requirements |
| 4.4 | Addition of safety related information |
| 4.8 | Addition of safety related information |
| 5.3 | Addition of preclinical safety data |