529108

Suprefact® 1 mg/ml Solution for Injection

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Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
SUPREFACT 1mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution for injection contains as active ingredient, 1.05mg buserelin acetate, equivalent to 1mg 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 per ml and 2.255mg sodium per ml.
For a full list of excipents, 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.

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(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 mcg/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 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. Contra-indications
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
Suprefact should only be used under the direction of a specialist having available appropriate facilities for monitoring the response to treatment. 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 with a history of depression must be monitored carefully 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).
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).
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 Suprefact.
The use of LHRH-agonists may be associated with decreased bone density and may lead to osteoperosis and an increased risk of bone fracture (see section 4.8). Particularly in patients with known risk factors for osteoperosis (e.g. chronic alcohol abuse, smokers, long-term therapy with anticonvulsants or corticosteroids or a family history of osteoperosis), periodic monitoring of bone mineral density (BMD) and use of preventative measures are recommended during therapy to prevent osteopenia/osteoperosis (risk of decreased bone density that may lead to osteoporosis and increased risk of bone fracture).
Prostatic carcinoma: Monitoring of the clinical effect of Suprefact 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 into 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 upon the spinal cord or CNS. Disease flare is prevented by the prophylactic use of an anti-androgen, e.g. cyproterone acetate, 300 mg daily. It is strongly recommended that administration of anti-androgen be started as adjunctive therapy about 5 days before the first dose of Suprefact and continued in parallel with buserelin for at least 3-4 weeks after commencement of Suprefact therapy. After this time testerone levels have usually fallen into the desired range in response to buserelin. If an anti-androgen is used over a period exceeding 2 weeks due attention should be paid to the contraindications and precautions associated with its prolonged use.
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 transient activation of the tumor and its metastases (see also under section 4.8 Undesirable Effects)
The effect can be monitored clinically and by determination of prostate specific antigen (PSA) and testosterone in the serum. Testosterone levels increase in the beginning of the treatment and thereafter decreases during two weeks. After two to four weeks, the testosterone levels have decreased to castration level.
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 that it is being 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. After the initial determination, testosterone levels should be monitored at 3-monthly intervals. A proportion of patients will have tumours that 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.
Adjunctive use in ovulation induction: Suprefact should be used under the care of a specialist with experience in the indication.
Before treatment is started, it is recommended that a pregnancy test be performed.
In-vitro fertilisation and induction of ovulation must 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.
Follicle recruitment may be increased especially in patients with PCOD. In patients with PCOD ovulation induction may be more difficult.
The combination of gonadotrophins with buserelin carries a higher risk of development of ovarian hyperstimulation syndrome (OHSS) than the use of gonadotrophins alone.
In patients with polycystic ovarian syndrome, caution is recommended, because there is an increased tendancy 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, oligurea, 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.
Each stimulation cycle must be monitored carefully to permit early identification of affected patients. If necessary, administration of human chorionic gonadotrophin (hCG) must be foregone.
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. Interactions with other Medicinal Products and other forms of Interaction
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Suprefact 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).
During treatment with buserelin, the affect of antidiabetic agents may be attenuated.
In concomitant treatment with sexual hormones, 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
In general: Buserelin treatment may lead to:
- Skin and subcutaneous tissue disorders: changes in scalp and body hair (increase or 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, leading to anaphylactic/anaphylactoid shock.

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Suprefact® 1 mg/ml Solution for Injection

buserelin (as buserelin acetate)

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Is this leaflet hard to see or read? Phone 01 403 5600 for help

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

What is in this leaflet

1. What Suprefact Injection is and what it is used for

Suprefact Injection contains a medicine called buserelin acetate. This belongs to a group of medicines called gonadotropin releasing hormone analogues. This is a synthetic version of a hormone that occurs naturally in the body. It works by lowering the production of sex hormones.
In men it is used to treat prostate cancer by lowering the amount of the hormone 'testosterone'.
In women it is used to complement ovulation induction (subcutaneous use only)

2. What you need to know before you use Suprefact Injection

Do not use this medicine and tell your doctor if:
× You are allergic (hypersensitive) to:
– buserelin
– other similar medicines such as goserelin
– any of the other ingredients of Suprefact Injection (listed in Section 6 below) Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
× You have a tumour that is not affected by changes in hormone levels
× You have had an operation to remove your testicles
× You are pregnant or breast-feeding. Before treatment begins a pregnancy test should be performed.
Do not use if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before using Suprefact Injection.

Warnings and Precautions
Check with your doctor or pharmacist before using your medicine if:
- You have depression. There have been reports of depression in patients taking Suprefact Injection which may be severe. If you are taking Suprefact Injection and develop depressed mood, inform your doctor.
- You have high blood pressure. Your blood pressure must be checked regularly
- You have or have had heart problems
- You have diabetes. You should check your blood glucose levels regularly
- You have metabolic bone disease or have additional risk factors for osteoporosis such as chronic alcohol abuse, smoking, a family history of osteoporosis or are on long-term medication for seizures or corticosteroids.
- You have polycystic ovarian syndrome, ovarian cysts have been observed in the initial phase of buserelin treatment.
- If you are using gonadotrophins (protein hormones). Combined use of buserelin with gonadotrophins may carry a higher risk of development of ovarian hyperstimulation syndrome (OHSS) than the use of gonadotrophins alone.
- You should also be taking medication that regulate your sex hormone levels (called anti-androgen e.g. cyptroterone acetate), if you are a male patient.

Studies suggest a relationship between gonadotropin-releasing hormone (GnRH) agonist treatment and increased risk of cardiovascular disease and diabetes mellitus. These risks should be evaluated before initiating and during therapy, and patients should be monitored and treated accordingly
If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before using Suprefact Injection.
- Please tell your doctor if you have any of the following: Any heart or blood vessel conditions, including heart rhythm problems (arrhythmia), or are being treated with medicines for these conditions. The risk of heart rhythm problems may be increased when using Suprefact Injection.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Suprefact Injection can affect the way some other medicines work. Also some medicines can affect the way Suprefact Injection works.
In particular, tell your doctor or pharmacist if you are taking the following:
- medicines for diabetes
- hormone-based medicines

Suprefact Injection might interfere with some medicines used to treat heart rhythm problems (e.g. quinidine, procainamide, amiodarone and sotalol) or might increase the risk of heart rhythm problems when used with some other drugs (e.g. methadone (used for pain relief and part of drug addiction detoxification), moxifloxacin (an antibiotic), antipsychotics used for serious mental illnesses).

Pregnancy, breast-feeding and fertility
Do not take this medicine is you are pregnant or think you may be pregnant. Do not breast-feed while you are taking this medicine.

Driving and using machines
You may feel dizzy, drowsy or have blurred eyesight while using this medicine. If this happens, do not drive or use any tools or machines.

Suprefact Injection contains
- **Benzyl alcohol** (10.000 mg/ ml): it must not be given to premature or newborn babies. Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old
- **Sodium:** This medicinal product contains less than 1mmol (23 mg) per dose, i.e. it is essentially 'sodium-free'.

3. How to use Suprefact Injection

Suprefact Injection is normally given by a doctor or nurse. This is because it needs to be given as an injection underneath the skin (subcutaneous injection).

How much Suprefact Injection is given
If you are not sure why you are being given Suprefact Injection or have any questions about how much Suprefact Injection is being given to you, speak to your doctor or nurse.

Treatment of prostate cancer:
- 0.5 ml of Suprefact Injection will be given to you every 8 hours for 7 days
- After 7 days of treatment, you will change to using a nasal spray

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Treatment for ovulation induction:
- 0.5 ml of Suprefact Injection once daily. Treatment should start on Day 1 of your period or if it is confirmed that you are not pregnant, on Day 21 of your cycle. In some patients dosage may vary.

It is very important to take your doses regularly every day. Therefore, administer the injections at equal intervals.

If you have more Suprefact Injection than you should
It is unlikely that your doctor or nurse will give you too much medicine. Your doctor and nurse will monitor your progress by testing your blood at regular intervals, and check the medicine you are given. Always ask if you are not sure why you are getting a dose of medicine.
The following effects may occur: feeling weak, headache, feeling nervous, hot flushes, feeling dizzy, feeling sick, stomach pain, swelling of the legs and breast pain. You may also have pain, bleeding or hardening of the skin at the site of injection.

If you miss a dose of Suprefact Injection
Your doctor or nurse will have instructions on when to give you this medicine. It is unlikely that you will not be given the medicine as it has been prescribed. However, if you do think you have missed a dose, tell your doctor or nurse.
If you are injecting this medicine yourself and you forget a dose, take it as soon as you remember it. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop having Suprefact Injection.
Keep using Suprefact Injection until your doctor tells you to stop.

Blood Tests
Using Suprefact Injection may affect the results of some blood tests. In particular, Suprefact Injection can change the level of liver enzymes and fats in the blood (lipids) shown up in blood tests. If you are going to have a blood test, it is important to tell your doctor you are using Suprefact Injection.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Suprefact can cause side effects, although not everybody gets them.

Stop using Suprefact and see a doctor or go to a hospital straight away if;
- You have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- You have leg pain, difficulty breathing or being short of breath and chest pain. This could be because of blood clots in your body and lungs
- You have pain, swelling or a feeling of tension in your stomach; feel sick or are sick, have gained weight, have diarrhoea, are having difficulty breathing or are short of breath or are passing less urine. These could be signs of a serious side effect called "Ovarian Hyperstimulation Syndrome (OHSS)"
- You are receiving 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.

Tell your doctor straight away if you notice any of the following serious side effects:
- You bruise more easily than usual. This could be because of a blood problem called 'thrombocytopenia'
- You get a lot of infections. Signs include fever, sore throat or mouth ulcers. These could be signs of a blood problem called leucopenia
- You have severe headaches and eyesight problems. This is very rare but if it happens it could be due to tumours on the pituitary gland. This gland is found at the base of the brain

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- Your blood pressure becomes higher. This is very rare but if it happens you may get symptoms such as crushing chest pain, confusion, problems with your eyesight, tiredness and an uneven heartbeat
- You have problems passing water (urine)
- You have sharp pain or aching in your side in the area between the ribs and the hips. These could be signs of a swollen kidney
- You feel tired and your body is swollen. These could be signs of fluid build up in the tissues called lymphostasis
- You feel tired, lack energy; have shortness of breath and palpitations. These could be symptoms of anaemia, a decrease in the number of red blood cells. Due to testosterone suppression, GnRH agonist therapy may increase the risk of anaemia. Patients should be evaluated for this risk and managed accordingly.

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days:

- Loss of sex drive (libido)
- In women, painful sexual intercourse.
- In men, atrophy (shrinking) of the testes
- Bone or muscle discomfort such as shoulder pain or stiffness or muscle weakness. If Suprefact Injection is used for a long period of time, it may increase the risk of you getting a condition called 'osteoporosis'. This is when your bones are more likely to break
- Lowered tolerance to glucose which may lead to worsening of existing diabetes
- Changes in body weight, changes in appetite and increased thirst
- Mood changes such as depression (feeling depressed) or worsening of depression: long term use: common, short term use: uncommon and feeling anxious.
- Feeling nervous, dizzy, tired or drowsy
- Headache and disturbed sleep
- Problems with memory and concentration
- Pain or redness at the injection site
- Unusual skin sensations such as numbness, tingling, pricking, burning or creeping on the skin. This can feel like 'pins and needles' (usually in the arms and legs) and is called paraesthesia
- Dry eyes (possibly leading to eye irritation in people who wear contact lenses), blurred eyesight, feeling of pressure behind the eyes
- Hearing problems such as ringing in the ears (tinnitus)
- Very fast, uneven or forceful heartbeat (palpitations)
- Facial swelling (puffiness) due to water retention which may also cause swollen arms or legs
- Feeling or being sick, stomach ache, pain in the lower abdomen, diarrhoea.
- Constipation
- Menopausal like symptoms and bleeding
- Dry skin, acne, hot flushes or increased sweating
- Hair grows more than normal (including body and facial hair)
- Hair loss (including body or facial hair)
- Splitting of nails
- Vaginal discharge, change in breast size, breast tenderness or milk production
- In women with uterine fibroids you may have worsening of your condition
- Changes in the level of liver enzymes, fats (lipids) and a substance called 'bilirubin' in the blood shown up in blood tests
- Frequency not known: Changes in ECG (QT prolongation)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly 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
By reporting side effects you can help provide more information on the safety of this medicine..

5. How to store Suprefact Injection

Keep this medicine in a safe place where children cannot see or reach it.
Do not use Suprefact Injection after the expiry date which is stated on the label and carton after 'EXP'.
The expiry date refers to the last day of that month.
Do not store above 25°C. Do not freeze. Store in the original container in order to protect from light.
Any material remaining after one week of first opening should be discarded
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Suprefact Injection contains

- Each 1 ml contains 1 milligram of the active substance, buserelin as buserelin acetate
- The other ingredients are sodium hydroxide, sodium chloride, sodium dihydrogen phosphate, benzyl alcohol and water for injections

What Suprefact Injection looks like and contents of the pack

Suprefact Injection a clear, colourless, solution for injection. Each vial contains 5.5 ml of solution.
It is available in boxes containing two multidose vials.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
sanofi-aventis Ireland Ltd., T/A SANOFI
Citywest Business Campus,
Dublin 24,
Ireland.
Tel: 01403 5600
Fax: 01403 5687
email: IEmedinfo@sanofi.com

Manufacturer
Sanofi-Aventis Deutschland GmbH,
Industriepark Höchst,
D-65926 Frankfurt am Main,
Germany

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in 06/2015.

- Investigations: changes in blood lipids, increase in serum levels of liver enzymes (e.g. transaminases), increase in bilirubin, weight changes (increase or decrease)
- 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".
- 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
- General disorders and administration site reactions: tiredness
- 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
- 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.
- Muscoskeletal 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 the duration of therapy.
- 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.

Pain or local reactions at the injection site are possible.
Prostatic carcinoma: At the beginning of treatment, a transient rise in the serum testosterone level usually develops and may lead to temporary activation of the tumour with secondary reactions such as:

- occurrence or exacerbation of bone pain in patients with bone metastases.
- signs of neurologic deficit due to tumour compression with e.g. muscle weakness in the legs.
- impaired micturition, hydronephrosis or lymphostasis.
- thrombosis with pulmonary embolism.

Such reactions can largely be avoided when an antiandrogen is given concomitantly in the initial phase of buserelin treatment (see also under section 4.4 Special Warnings and Precautions for use)
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, atrophy of the testes and loss of potency and libido (in most patients; result of hormone deprivation), usually painless gynaecomastia (occasionally) as well as mild oedemas of the ankles and lower legs may occur.
Preparation for 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 additional manifestations of inhibited oestrogen production, in most cases uterine bleeding ("period") occurs during the first weeks of treatment. Uterine bleeding may also occur in the further course of treatment.
As additional manifestations 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. A decrease in bone mineral content, the magnitude of which relates to the duration of therapy, occurs in women 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 phosphates may occur. These are reversible on discontinuing treatment.
Very rare cases of pituitary adenomas were reported during treatment with LH RH agonists including buserelin.
Further adverse effects are not clearly attributable to hormone deprivation; increase or decrease in breast size with breast tenderness, splitting nails, acne, dry skin, vaginal discharge (occasional), oedema of the face and extremities (occasional). In addition, lactation, stomach ache, lower abdominal pain, paraesthesiae (especially in the arms and legs) may occur, as may dryness of the eyes, which may lead to eye irritation in wearers of contact lenses.
It is recommended to stop Suprefact treatment at the start of hCG treatment.
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.
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.
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 4.4 Special warnings and Precautions for Use)
Degeneration of uterine fibroids in women with uterine fibroids.

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, ACTH, 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 200 micrograms 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 5.5ml multidose vial.
Each vial consists of clear, colourless, Type I (PhEur) 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.

8. MARKETING AUTHORISATION NUMBER

PA 540/74/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 1986
Date of last renewal: 16th August 2009

10. DATE OF REVISION OF TEXT

July 2015.

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