PRODUCT MONOGRAPH

PrSUPREFACT®

Buserelin injection, 1 mg/mL

Buserelin nasal solution, 1 mg/mL

and

PrSUPREFACT® DEPOT 2 months

Buserelin acetate implant, buserelin 6.3 mg

Luteinizing Hormone-Releasing Hormone (LH-RH) Analogue

Hoechst Marion Roussel Canada Inc.
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H7L 4A8

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PHARMACOLOGIC CLASSIFICATION

Luteinizing Hormone-Releasing Hormone (LH-RH) Analogue

ACTION AND CLINICAL PHARMACOLOGY

Buserelin acetate is a synthetic peptide analogue of the natural gonadotropin releasing hormone (GnRH/LH-RH). The substitution of glycine in position 6 by D-serine, and that of glycinamide in position 10 by ethylamide, leads to a nonapeptide with a greatly enhanced LH-RH effect. The effects of buserelin on follicle stimulating hormone (FSH) and luteinizing hormone (LH) release are 20 to 170 times greater than those of LH-RH. Buserelin also has a longer duration of action than natural LH-RH.

Investigations in healthy adult males and females have demonstrated that the increase in plasma LH and FSH levels persist for at least 7 hours and that a return to basal values requires about 24 hours.

Clinical inhibition of gonadotropin release, and subsequent reduction of serum testosterone or estradiol to castration level, was found when large pharmacologic doses (50-500 mcg SC/day or 300-1200 mcg IN/day) were administered for periods greater than 1 to 3 months. Chronic administration of such doses of buserelin results in sustained inhibition of gonadotropin production, suppression of ovarian and testicular steroidogenesis and, ultimately, reduced circulating levels of gonadotropin and gonadal steroids. These effects form the basis for buserelin use in patients with hormone-dependent metastatic carcinoma of the prostate gland.

In the clinical pharmacology studies with SUPREFACT® DEPOT 2 months (buserelin acetate implant), the time-concentration curves of buserelin release from implants were reproducible and similar to those observed in preclinical studies. Maximum release on day 1 was followed by an extended plateau phase which lasted for eight weeks. After this period, an accelerated biodegradation of the implant material was observed with a terminal half-life of release of 20-30 days. The single dose studies performed in healthy male subjects and in patients with benign

prostatic hypertrophy showed a therapeutic release rate for eight weeks (dosage interval); a minimum therapeutic release rate of 4.95 μg/day after 8 weeks was fully effective in maintaining testosterone levels in the surgical castration range by controlled release of buserelin. At the end of the dosage interval, the average fraction of the buserelin dose released from the implants based on urinary excretion data was 84% (in healthy subjects) and 92% (in patients with benign prostatic hypertrophy). Chronic administration of the implant every two months ensures continuous suppression of testosterone secretion with no cumulation of buserelin release after repeated dosing.

INDICATIONS AND CLINICAL USE

SUPREFACT® (buserelin acetate injection and nasal solution) and SUPREFACT® DEPOT 2 months (buserelin acetate implant) are indicated for the palliative treatment of patients with hormone-dependent advanced carcinoma of the prostate gland (Stage D).

CONTRAINDICATIONS

SUPREFACT® (buserelin acetate injection and nasal solution) and SUPREFACT® DEPOT 2 months (buserelin acetate implant) are contraindicated in: patients with known hypersensitivity to buserelin or any other formulation component [See `PHARMACEUTICAL INFORMATION']; patients who do not present with hormone-dependent carcinoma; and in patients who have undergone orchiectomy (in these patients, no further reduction of testosterone level is to be expected with buserelin therapy).

WARNINGS

General

Cases of early, transient exacerbation of disease signs and symptoms have been reported during treatment with LH-RH agonists [See `PRECAUTIONS'].

The majority of clinical studies demonstrating the efficacy of SUPREFACT® (buserelin acetate injection and nasal solution) were completed without concomitant therapy with antiandrogens during the first weeks of treatment. For the clinical studies with SUPREFACT® DEPOT 2 months, however, an antiandrogen was administered as initial concurrent treatment for a duration of five weeks, starting seven days before the start of buserelin implant therapy. At the start of treatment, there is a temporary rise in male sex hormones. In a few patients, this rise may be associated with isolated cases of short-term worsening of signs and symptoms such as bone pain, urinary signs and symptoms (usually occurring in patients with a previous history of obstructive uropathy) or muscular weakness in the legs. Worsening of clinical conditions may occasionally require discontinuation of therapy and/or surgical intervention.

Patients with vertebral metastases:
Due to the possibility of early, transient, lesion exacerbation, and consequent possible spinal cord compression, these patients should be closely monitored when LH-RH agonist treatment is initiated.

Patients with genitourinary tract symptoms:
Patients with genitourinary symptoms may experience a transient increase in such symptoms early in LH-RH agonist treatment. These patients should be particularly closely observed for events indicative of obstruction.

Reversibility of LH-RH agonist-induced hypogonadism:
While hypogonadism is a pharmacologic consequence of long-term LH-RH agonist treatment, its reversibility has not been established in patients suffering with prostatic carcinoma.

PRECAUTIONS

Transient exacerbation of disease signs and symptoms:
The administration of LH-RH agonists is occasionally related with early, transient (less than 10 days duration usually) exacerbation of the signs and symptoms of metastatic prostatic cancer which sometimes occurs in association with a transient rise in serum testosterone. Special precautions are recommended in the following patients since symptoms may progress to warrant, in rare cases, additional or alternate interventions:
- patients with metastatic vertebral lesions,
- patients with history of obstructive uropathy [See 'WARNINGS'].
From clinical trials with SUPREFACT® DEPOT (buserelin acetate implant), administration of an antiandrogen before and concurrently at the start of buserelin implant therapy may avoid the occurrence of such signs and symptoms of the disease (in clinical trials, the antiandrogen was primarily given for the first five weeks, beginning seven days prior to the first buserelin implant injection).

Monitoring of patients:
Regular clinical assessment of patients is recommended and should include clinical laboratory determinations of serum testosterone, prostatic acid phosphatase or acid phosphatase and prostate-specific antigen (PSA). If cancer is responsive to buserelin acetate therapy, the prostate cancer tumor markers (PAP and PSA), if elevated prior to the commencement of treatment, are usually reduced by the end of the first month.

The status of bone lesions may be monitored by bone scans and that of the prostate lesions may be followed by ultrasonography and/or CT scan in addition to digital rectal examination.

Evaluation for obstructive uropathy may be undertaken by ultrasonography, intravenous pyelogram or CT scan in addition to clinical examination. In addition, it is recommended that serum testosterone levels be determined after 4 to 6 weeks of treatment with LH-RH agonists and then at 3-monthly intervals. Inadequate serum testosterone suppression should lead to evaluation of patient compliance.

Patients with a history of depression or depressed moods should be observed closely for evidence of mood changes and treated accordingly.

In treated hypertensive patients, hypertensive crisis may occur. It is recommended that blood pressure be monitored regularly in these patients.

Isolated cases of loss of diabetic control have been observed. Blood glucose levels should be checked regularly in diabetic patients.

Changes in bone density:
Bone loss can be expected as part of natural aging and can also be anticipated during medically induced hypoandrogenic status caused by long term use of LH-RH agonists such as buserelin acetate. In patients with significant risk factors for decreased bone mineral content and/or bone mass such as family history of osteoporosis, chronic use of corticosteroids or anticonvulsants or chronic abuse of alcohol or tobacco, LH-RH agonists may pose additional risk. In these patients, risk and benefits must be weighed carefully before initiation of LH-RH agonist therapy.

Effect on clinical laboratory tests:
LH-RH agonist treatment will affect selected hormonal and other serum/urine parameters in the first week of treatment: elevation of testosterone and dihydrotestosterone, as well as acid phosphatase can be expected. With chronic drug administration, these elevated values of these variables will fall below baseline.

Renal function tests, blood urea nitrogen and creatinine may rarely be elevated during the first few days of LH-RH agonist therapy in prostate cancer patients before returning to normal.

Drug interactions:
During treatment with buserelin, the effect of antidiabetic agents may be attenuated [see also 'ADVERSE REACTIONS'].

Allergic reactions:
Allergic asthma with dyspnea as well as in isolated cases, anaphylactic/ anaphylactoid shock have been observed in patients treated with buserelin, necessitating early treatment of such conditions. For patients experiencing anaphylactic/anaphylactoid reactions who were given SUPREFACT® DEPOT, it may be necessary to surgically remove the implant.

ADVERSE REACTIONS

The adverse effects observed in patients treated with SUPREFACT® (buserelin acetate injection and nasal solution) and SUPREFACT® DEPOT (buserelin acetate implant) are, principally, directly related to its anticipated pharmacologic action, i.e. suppression of pituitary (gonadotropin) and gonadal (testosterone) hormone production with resulting clinical signs and symptoms of hypogonadism (hypoandrogenism).

An early in treatment transient increase in serum testosterone levels usually occurs. Occasionally, this may be associated with transient worsening of clinical status and secondary reactions such as: occurrence or exacerbation of bone pain in patients with bone metastases, signs of neurological deficit due to tumour compression, impaired micturition, hydronephrosis, lymphostasis or thrombosis with pulmonary embolism. This transient initial rise in serum androgen will be followed by a progressive decrease to castration levels. [See `WARNINGS/PRECAUTIONS'].

In patients treated with SUPREFACT® DEPOT, such reactions can be avoided when an antiandrogen is given concomitantly in the initial phase of buserelin treatment [see 'PRECAUTIONS']. Some of these patients may, nevertheless, develop a mild, transient increase in tumor pain and a deterioration in general well-being.

Long-term treatment with LH-RH agonists may, in isolated cases, lead to development of pituitary adenomas; in humans, however, this has not yet been observed with buserelin therapy.

SUPREFACT® injection and nasal solution.
Serious clinical flare reactions were reported in approximately 1% of patients in SUPREFACT® efficacy trials.

In a large, North American multicentre study of SUPREFACT®, the following adverse reactions were encountered:

Patients receiving daily subcutaneous injection SUPREFACT®: 71.6% reported hot flushes, 84.8% reported loss of libido, 79.4% reported impotence. However, more than 50% of all buserelin subjects reported loss of libido and impotence at admission.

For patients receiving intranasal SUPREFACT®: 66.1% reported hot flushes, 75.0% reported loss of libido, 75.0% reported impotence, 12.5% reported nasal irritation and 28.5% reported headache. Not all cases were considered to be SUPREFACT® related.

Other adverse reactions considered to be SUPREFACT® related and occurring in more than 1% of patients were: gynaecomastia, pruritus and gastrointestinal disturbances.

Of patients who received maintenance SUPREFACT® therapy by the daily subcutaneous injection route, 11.9% reported one or more generally transient injection site reactions: pain (4.6%), irritation (3.3%), swelling (3.3%), urticaria (2.0%) and other (4.6%). None of the reactions were severe or required discontinuation of therapy.

Other adverse reactions, arranged by body system, possibly or probably related to the administration of SUPREFACT® (individual signs/symptoms not marked with an asterisk occurred at an incidence below 1%; * = incidence between 1% and 2%) included:

Body as a whole:* (daily subcutaneous injection SUPREFACT® only) Clinical flare reaction*, fever, pain
Digestive system:* (daily subcutaneous injection SUPREFACT® only) Diarrhoea, nausea
Endocrine system: (daily subcutaneous injection SUPREFACT® only) Feminization
Nervous system: *(daily subcutaneous injection and intranasal* SUPREFACT®) Dry mouth*, (intranasal SUPREFACT®" only), increased sweating* (intranasal SUPREFACT® only), hot flushes (*intranasal SUPREFACT®, <1% daily subcutaneous injection SUPREFACT®)
Respiratory system: (intranasal SUPREFACT® only) Dry nose*
Skin and appendages: (daily subcutaneous injection SUPREFACT® only) Gynaecomastia*, hirsutism
Urogenital system: (daily subcutaneous injection SUPREFACT® only) Urinary retention

SUPREFACT® DEPOT 2 months
No serious clinical flare reactions were reported in patients (n=297) enrolled in clinical studies with SUPREFACT® DEPOT 2 months.

In an open-label, non-comparative, international multicentre study of SUPREFACT® DEPOT 2 months comprising a total of 241 patients, the following adverse reactions considered to be remotely, possibly or probably related to SUPREFACT® DEPOT 2 months were encountered during one year of treatment: 15.8% reported hot flushes, 2.5% reported libido decreased, 1.2% reported impotence, 1.2% reported injection site pain, hypertension [including hypertensive crises in treated hypertensive patients] (2.9%), depression (2.9%) and oedema of the ankles and calves (2.1%).

Other adverse reactions, arranged by body system, and remotely, possibly or probably related to the administration of SUPREFACT® DEPOT 2 months (individual signs/symptoms occurred at an incidence of less than 1%) were:

Body as a whole: Non-serious clinical flare reaction, fever, pain
Cardiovascular system: Heart failure, palpitations, tachycardia, thrombosis
Digestive system: Constipation, nausea
Endocrine system: Exacerbation of a pre-existing diabetes mellitus, hyperglycaemia
Musculoskeletal system: Arthritis
Metabolic and nutritional disorders: Weight gain, weight loss
Nervous system: Headache, hyperalgesia, sleep disorder (insomnia), sweating increased
Respiratory system: Pharyngitis
Skin and appendages: Eczema, gynaecomastia, injection site pain, injection site reaction, pruritus, rash
Special senses: Blindness in one eye (temporary)
Urogenital system: Abnormal ejaculation

Miscellaneous
In the international database, other adverse events, including events which were observed only in females (excluding female gender-specific events) or for other unlabelled indications, have been observed in patients treated with buserelin, as itemized below (not all events were considered to be related to buserelin therapy):

Digestive system: Changes in appetite (e.g. anorexia), increased thirst, vomiting
Haemic and lymphatic system: Leucopenia, thrombopenia
Laboratory values: Changes in blood lipids (e.g. hypercholesterolemia, hyperlipidemia), increase in bilirubin levels, increase in serum liver enzymes levels (e.g. transaminases)
Nervous system: Concentration and memory disturbances, dizziness, drowsiness, emotional instability, feelings of anxiety, mood changes, nervousness, tiredness
Skin and appendages: Articular pains, irritation of the mucosa in the nasopharynx due to nasal solution administration (which may lead to nosebleeds, hoarseness, disturbances of smell or taste), rhinorrhea, skin reaction (wheal) allergy
Special senses: Eye dryness and irritation, feeling of pressure behind the eyes, impaired vision (e.g. blurred vision), hearing disorders, tinnitus

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no clinical reports of acute overdosage with SUPREFACT® (buserelin acetate injection and nasal solution) or SUPREFACT® DEPOT 2 months (buserelin acetate implant).

From acute studies of buserelin acetate in rodents, neither 0.5 mg/kg/IV (mouse) nor 1 mg/kg/IV (rat) produced evidence of toxic signs.

Two groups of 6 and 4 healthy volunteers, aged 26-40 years and 31-40 years respectively, were given 1 mg buserelin or 5 mg buserelin **orally** as a single dose. No LH or FSH release was observed. No clinical effects were observed.

DOSAGE AND ADMINISTRATION

SUPREFACT® (buserelin acetate injection and nasal solution) and SUPREFACT® DEPOT 2 months (buserelin acetate implant) should be administered at approximately equal time intervals to ensure that the desired therapeutic effect is maintained.

SUPREFACT® injection and nasal solution.

Initial treatment:
For the first seven days of treatment give SUPREFACT® 500 mcg (0.5 mL) every 8 hours by subcutaneous injection. For patient comfort, vary the injection site [See 'INFORMATION FOR THE PATIENT'].

Maintenance treatment:
Depending upon patient preference, or physician recommendation, maintenance treatment may be by daily subcutaneous injection or by intranasal administration three times daily.
During maintenance dosing by the subcutaneous injection route, the SUPREFACT® dose is 200 mcg (0.2 mL) daily. For patient comfort, vary the site of injection [See 'INFORMATION FOR THE PATIENT'].

During maintenance dosing by the intranasal administration route, the SUPREFACT® dose is 400 mcg (200 mcg into each nostril) three times daily using the metered-dose pump (nebulizer) provided. Each pump action delivers 100 mcg buserelin acetate or 0.1 mL solution [See 'INFORMATION FOR THE PATIENT'].

SUPREFACT® DEPOT 2 months.

Implant dosing:
The contents of one applicator, consisting of two implant rods, equivalent to a total of 6.3 mg buserelin, is injected subcutaneously every two months into the lateral abdominal wall. Before injection, a local anaesthetic may be used if desired. It is important to maintain a regular, two-month rhythm for the dosage interval. In exceptional cases, the dosage interval may be shortened or extended by a few days.

The applicator containing the implant rods should be kept horizontal before injection [See 'INSTRUCTIONS FOR USE'].

SUPREFACT® DEPOT 2 months is intended for the long-term treatment of prostatic carcinoma.

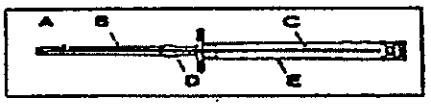
Initial antiandrogen comedication:
About seven days before the first injection of SUPREFACT® DEPOT 2 months, an antiandrogen should be administered in accordance with the manufacturer's directions. This comedication is to be continued for four weeks after the first SUPREFACT® DEPOT 2 months injection, when testosterone levels can be expected to have entered the surgical castration range.

INSTRUCTIONS FOR USE
SUPREFACT® DEPOT 2 months (buserelin acetate implant)

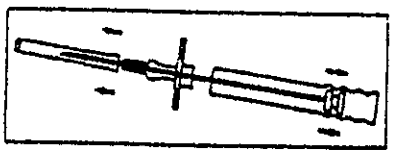
INSTRUCTIONS FOR USING THE APPLICATOR

Please note: To prevent the implant rods from falling out of the injection needle, hold the applicator in a vertical position until immediately prior to puncture, with the needle pointing upwards.

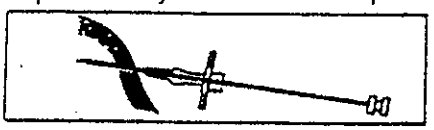
1. After removing the applicator from the foil wrapping, check that both implant rods are located in the window of the handle. If necessary, tap the protective cap of the needle lightly to reposition them in the window.



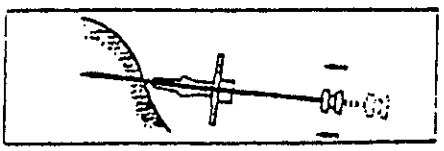
2. Disinfect the injection site of the lateral abdominal wall and administer a local anaesthetic, if desired. After removing the protective case from the plunger (E), remove the cap from the injection needle (B).



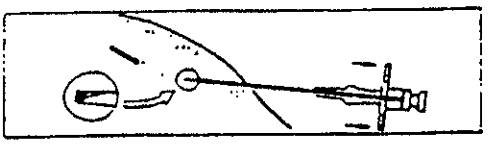
3. Lift a fold of skin and insert the needle approximately 3 cm (somewhat more than 1 inch) into the subcutaneous tissue, with the tip of the needle pointed slightly upwards. Withdraw the applicator about 1 to 2 cm prior to injection of the implant rods.



4. While fully depressing the plunger, inject the implant rods into the subcutaneous tissue. Compress the puncture channel while withdrawing the needle so that the implant rods are retained in the tissue.



5. To ensure that both implant rods have been injected, check the tip of the plunger to see if it is visible at the tip of the needle.



A - Needle; **B** - Protective cap of needle; **C** - Plunger;
D - Implant rods; **E** - Protective cap of plunger.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

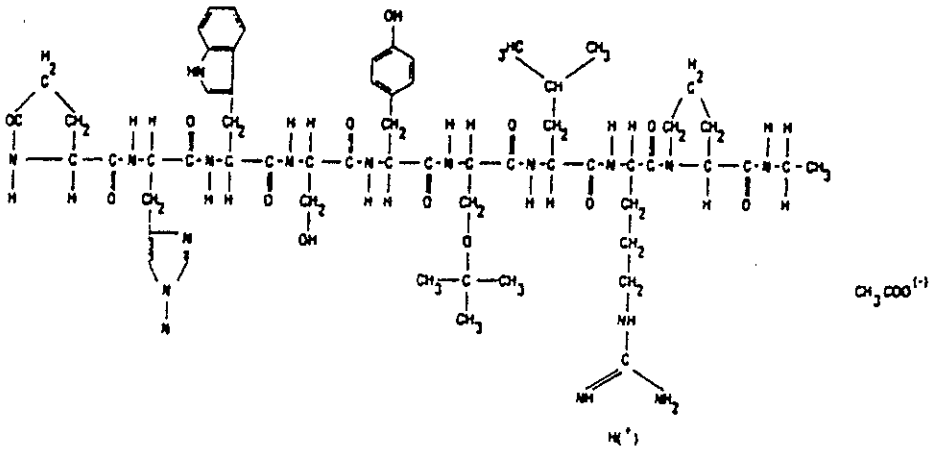
Proper name: Buserelin acetate (USAN)

Chemical name: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-O-tertiar butyl-seryl-L-leucyl-L arginyl-L-prolin-ethylamide-acetate

or

(D-Ser[Tbu]^{6}-des-Gly-$NH_2{}^{10}$)LH-RH ethylamide

Structural formula:



Molecular weight: 1299.5

Molecular formula: $C_{62}\ H_{90}\ N_{16}\ O_{15}$

Physical form: An amorphous, white substance

Solubility: Freely soluble in water and dilute acids

Reactivity: Weak base

DOSAGE FORMS

COMPOSITION:

Solution for daily subcutaneous injection.
Each mL of sterile aqueous injection solution contains: 1.05 mg buserelin acetate (equivalent to 1.00 mg pure anhydrous buserelin free base), 10 mg benzyl alcohol as preservative, sodium chloride for tonicity adjustment, sodium hydroxide for pH adjustment and monobasic sodium phosphate buffer..

Solution for intranasal administration.
Each mL of aqueous intranasal solution contains: 1.05 mg buserelin acetate (equivalent to 1.00 mg pure anhydrous buserelin free base), 0.10 mg benzalkonium chloride as preservative, sodium chloride for tonicity adjustment, and citric acid/sodium citrate buffer.

Implant for subcutaneous injection.
Each applicator contains one implant dose consisting of two identical cream-coloured, biodegradable and biocompatible rods. Each implant dose contains a total of 6.6 mg buserelin acetate, equivalent to 6.3 mg buserelin base, and 26.4 mg poly-(D,L-lactide-co-glycolide) in a 75:25 molar ratio.

STABILITY AND STORAGE RECOMMENDATIONS:

Solution for daily subcutaneous injection.
Store at room temperature, below 25°C in the original container. DO NOT FREEZE, DO NOT EXPOSE TO SOURCES OF HEAT and do not use beyond the expiration date printed on the container label.

Solution for intranasal administration.
Store at room temperature, below 25°C in the original container. DO NOT FREEZE, DO NOT EXPOSE TO SOURCES OF HEAT and do not use beyond the expiration date printed on the container label.

There is no information available on possible incompatibilities between SUPREFACT® (buserelin acetate injection) or SUPREFACT® (buserelin acetate nasal solution) and other agents.

Implant for subcutaneous injection.
Store the intact package between 15°C-30°C. DO NOT FREEZE, PROTECT FROM HEAT and do not use beyond the expiration date printed on the container label.

AVAILABILITY OF DOSAGE FORMS:

Solution for daily subcutaneous injection.
SUPREFACT® (buserelin acetate) is packaged in clear glass multi-dose vials of 5.5 mL (net) ready for administration direct from the container. It is supplied in cartons of 2 x 5.5 mL.

Solution for intranasal administration.
SUPREFACT® is packaged in amber glass bottles of 10.0 mL (net) for intranasal administration via the metered-dose pump (nebulizer) provided. SUPREFACT® solution for intranasal administration is provided ready for administration direct from the container. It is supplied in cartons of 4 x 10.0 mL bottles and 4 metered-dose pumps.

The metered-dose pump (nebulizer) provided has a mechanical action and contains no propellants. Refer to "INFORMATION FOR THE PATIENT" for details on pump operation.

Implant for subcutaneous injection.
SUPREFACT® DEPOT 2 months is packaged in a sterile ready-to-use disposable applicator with an integrated needle (internal needle diameter of 1.4 mm) for subcutaneous injection. Each carton is supplied with one sterile foil bag containing one applicator pre-filled with one implant dose consisting two identical rods, each of 3.3 mg buserelin acetate.

INFORMATION FOR THE PATIENT

KEEP MEDICINES OUT OF REACH OF CHILDREN.

SUPREFACT® (buserelin acetate injection and nasal solution) or SUPREFACT® DEPOT 2 months (buserelin acetate implant) has been prescribed for you by your doctor and the information provided below is intended to assist you in the safe and effective use of this treatment. This information is not intended to supersede the instructions you have received from your doctor: they should be carefully followed. Any difficulties you encounter should be discussed with your doctor, or pharmacist.

SUPREFACT® Injection

This product, SUPREFACT® (buserelin acetate injection), should be kept at room temperature, below 25°C. Do not permit the product to freeze and do not expose it to sources of heat. Do not use SUPREFACT® beyond the expiry date printed on the label.

It is important that you follow-up your doctor's instructions carefully and it is also important that your treatment be assessed by your doctor on a regular basis.

SUPREFACT® treatment results in suppression of your sex hormones. Consequently, the complaints you may experience may be related to this hormone-suppressing action of the drug. Your complaints may include hot flushes and loss of sex drive. In rare instances, you may experience an increase in your disease process such as pain, or increased pain, or increased difficulty in urinating. Should you experience events such as these, contact your doctor without delay. Occasionally, reddening, itching or swelling may occur at the SUPREFACT® injection site. These occurrences can be minimized by rotating the site of injection. In the event of persisting problems of this nature consult your doctor. Do not make any changes in your treatment programme without first discussing the intended change with your doctor.

Administration:
The SUPREFACT® vial is supplied with a plastic cap which can be removed by pressing upwards with the thumb. This cap serves to ensure that the vial has not been previously entered. After removal (the cap can be discarded) the rubber diaphragm of the vial is exposed. Proceed:

1. Wash your hands, with soap and water, and dry on a clean towel.

2. Clean the rubber diaphragm of the SUPREFACT® vial with a cotton swab previously dipped in alcohol. Leave to dry.

3. Select an appropriate sterile, disposable syringe and needle assembly (your doctor or pharmacist will help you select a syringe of appropriate bore and cylinder graduations) and remove it from its sterile packaging.

4. Draw the syringe piston as far back as the volume (see syringe cylinder graduation) of solution you wish to withdraw from the vial.

5. Remove the needle sheath (protector).

6. Without touching the needle with your fingers, push the needle through the centre of the rubber diaphragm of the vial.

7. Push on the syringe plunger so that the selected air volume is expelled into the vial.

8. Keeping the needle in the vial, invert the vial into the vertical position adjusting the needle tip to a position below the surface of the solution in the vial.

9. Draw the required solution from the vial by withdrawing the syringe piston.

10. Carefully withdraw the needle and syringe assembly from the vial.

11. Choose your injection site (vary the site for each injection as discussed with your doctor or pharmacist) and clean the skin with an alcohol impregnated swab.

12. Pinch the site, if you wish, between index finger and thumb and, with the needle at an angle introduce the needle quickly under the skin as far as possible.

13. Withdraw the syringe piston a little and, if no blood is withdrawn into the syringe, then push on the piston steadily to inject the solution.

14. Upon completion of the injection, and resting the alcohol-impregnated swab over the needle entry site, remove the needle in a reverse fashion of the entry motion. Hold swab to injection site for a few seconds, then remove.

15. Discard needle and syringe assembly along with the swab in a safe manner. Return the SUPREFACT® vial to its storage area.

If you are taking SUPREFACT® by injection three times each day, try and space the injections eight (8) hours apart. If you are taking SUPREFACT® injection once daily administer it at the

same time of day every day. Should you forget to take a dose, administer it as soon as you remember.

SUPREFACT® Nasal Solution

This product, SUPREFACT® (buserelin acetate nasal solution), should be kept at room temperature, below 25°C. Do not permit the product to freeze and do not expose it to sources of heat. Do not use SUPREFACT® beyond the expiry date printed on the label.

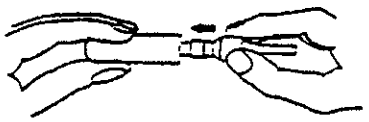
It is important that you follow your doctor's instructions carefully and it is also important that your treatment be assessed by your doctor on a regular basis.

SUPREFACT® treatment results in suppression of your sex hormones. Consequently, the complaints you may experience may be related to this hormone-suppressing action of the drug. Your complaints may include hot flushes, and loss of sex drive. In rare instances, you may experience an increase in your disease process such as pain, or increased pain, or increased difficulty urinating. Should you experience events such as these, contact your doctor without delay. Occasionally headaches may be troublesome and nasal irritation or dryness may appear. In the event of persisting problems consult your doctor. Do not make any changes in your treatment programme without first discussing the intended change with your doctor.

Administration:
The SUPREFACT® bottle is supplied in a carton complete with the required administration device, a metered-dose pump (nebulizer) which has a mechanical (spring-loaded) action. The pump contains no chemical propellants. To administer the SUPREFACT® using this pump proceed as follows, bearing in mind that these instructions are not intended to supersede instructions you may have received from your doctor:

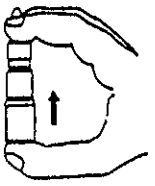
1. Wash your hands with soap and water and dry on a clean towel.

2. Remove the dose pump from the enclosed transparent plastic container; pull off both protective caps on top and bottom carefully.



3. Remove SUPREFACT® bottle from the container. Unscrew cap and discard it. Securely screw dose pump into glass bottle. The interior of the bottle is tapered towards the bottom. That feature, along with the concaved end to the pump tube, means that the pump can still usefully operate even though small quantities of solution (drug) remain. Do not tilt bottle when using the pump.

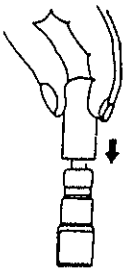
4. Before first application, hold bottle with pump in a vertical position and pump several times until a uniform mist is released.



This pump-priming may be necessary again after the pump has been stored between use.

5. Keeping the pump and bottle in a vertical position, place the pump aperture or nozzle into the nostril (if necessary, clean the nose prior to SUPREFACT® administration) and operate as before, once. Gentle sniffing aids the distribution of SUPREFACT® over the nasal passages from where it is absorbed. Nasal congestion will not prevent SUPREFACT® absorption/use.

6. After use, the pump remains in the bottle with its protective cap in position. Store bottle in an upright position at room temperature (below 25°C) avoiding exposure to sources of heat.



7. Follow your doctor's instructions closely. Do not make any changes in the treatment pattern unless you have first discussed the subject with the doctor.

SUPREFACT® DEPOT 2 months

This product, SUPREFACT® DEPOT 2 months (buserelin acetate implant), should be kept between 15°C-30°C in the original container. Do not permit the product to freeze and do not expose it to sources of heat. Do not use SUPREFACT® DEPOT 2 months beyond the expiry date printed on the label.

SUPREFACT® DEPOT 2 months is administered to you by your doctor or under supervision of a doctor once every two months. It is important that you follow-up your doctor's instructions carefully and it is also important that your treatment be assessed by your doctor on a regular basis.

SUPREFACT® DEPOT 2 months is a drug containing 6.3 mg of buserelin in a white-cream coloured cylindrical rod-shaped implants. SUPREFACT® DEPOT 2 months treatment results in

suppression of your sex hormones. Consequently, any complaints you may experience may be related to this hormone-suppressing action of the drug. Your complaints may include hot flushes and loss of sex drive. In rare instances, you may experience an increase in your disease process such as pain, or increased pain, or increased difficulty urinating. Should you experience events such as these, contact your doctor without delay. Occasionally, a local skin reaction may occur at the injection site such as itching, redness, burning and swelling. These reactions are mild and disappear after a few days. In the event of persisting problems of this nature, consult your doctor.

Do not make any changes in your treatment programme without first discussing the intended change with your doctor. If you forget to have SUPREFACT® DEPOT 2 months administered on the specified day, once every two months, have it administered as soon as you can. If you need more information, ask your doctor.

PHARMACOLOGY

ANIMAL PHARMACOLOGY

General

In anaesthetized dog, buserelin (1 or 10 mcg/kg/IV) had no significant effect on blood pressure, left ventricular pressure, cardiac contractility, heart rate, ECG, or arterial (femoral) flow.

In dog and rat, buserelin (10 mcg/kg/SC) had no significant saluretic or diuretic effect.

In rabbit, buserelin (10 mcg/kg/SC) had no significant effect on blood sugar.

In guinea pig isolated ileum, buserelin 10 mcg/mL (medium) had no spasmogenic effect and did not relax contractions caused by carbachol, histamine, or barium.

Buserelin (10 mcg/mL Ringer solution bath) had no significant contractile effect on isolated rat uterus.

Behavioural changes were not observed in conscious mouse administered buserelin (1 mg/kg/SC) for one week.

Special

Animal: in-vitro
The LH response was studied on a perfused column of isolated anterior pituitary cells from male rats. After a single pulse of LH-RH, LH output returned to basal levels in 8 minutes. After buserelin, the output lasted 20 minutes.

In-vitro, Leydig cells from hypophysectomized rats showed a 2-fold increase in testosterone responsiveness to buserelin compared to cells from intact rats. Isolated Leydig cells have high affinity sites for buserelin, similar in affinity to receptors in the anterior pituitary. Their short-term stimulation increases testosterone production, while long-term stimulation inhibits testicular function.

In isolated luteal cells buserelin reduced basal progesterone production and inhibited the stimulatory effect of HCG. Specific high-affinity binding of buserelin was observed in dispersed luteal cells, membrane-rich particles from luteinized rat ovary, and rat ovarian granulosa cell membrane preparation.

Animal: In-vivo

RAT

In male rats, 2.5, 5, 25 or 50 ng/80-100 g bw/SC buserelin produced peak plasma LH/FSH increases within 2 hours. Buserelin was 19 times more potent than natural LH-RH in releasing LH and 16 times more potent in releasing FSH. Buserelin can directly stimulate testosterone secretion by Leydig cells. When buserelin was injected in 55-day old male rats which had been hypophysectomized 3 days earlier, testosterone levels in serum rose to levels similar to those in intact untreated rats of the same age.

Male rats given buserelin 500 ng/day/SC/14 days showed serum LH and testosterone (T) stimulation at day 1 followed by blunted LH response, and absent T response at day 7 and 14. Animals given same daily dose by SC infusion showed day 1 LH and T response to be relatively blunted with absent response at day 7 and 14.

Groups of 10 initially immature rats were given buserelin 0.05, 0.1 or 0.2 mg/kg/SC/day for 28 consecutive days. Testicular weight and plasma testosterone level were reduced, compared to controls. Continuous infusion for 6 days of buserelin in doses of less than 340 ng/day in male rats led to an increase in pituitary LH-RH receptor numbers; when the daily dose was increased 10-100 fold pituitary LH-RH receptors were progressively down-regulated.

In immature female rats, pretreated with pregnant mare serum gonadotropin (PMSG), ovulation was induced by the intravenous injection of 3 ng of buserelin. The equi-effective dose of natural LH-RH was 130 times larger.

A luteolytic effect of buserelin was shown in rats made pseudopregnant with PMSG and human chorionic gonadotropin (HCG) using 50 ng subcutaneously from day 6 to day 9 of pseudopregnancy. Buserelin lowered serum progesterone level, ovarian ascorbic acid concentration and ovarian HCG binding. In mated rats, buserelin prevented pregnancy.

Adult male rats were given 0, 2.5 or 12.5 mcg/kg/day/SC or 5 or 25 mcg/kg/ twice weekly/SC buserelin for 12 months. Body weight was unaffected. The low daily dose significantly ($p < 0.05$) reduced the weight of testes and seminal vesicles. The high daily dose significantly reduced weights of testes, ventral prostate, seminal vesicles and levator ani muscle. Twice weekly, high-dose alone significantly reduced the weight of seminal vesicles only. Prostate weight was suppressed by daily dosing but returned to control values after a 5 month buserelin-free period.

In single dose rat studies, adult male Wistar rats (total n= 42) were administered SC implants containing 3.3 mg buserelin acetate and poly-(D,L-lactide-co-glycolide) [PLG] in a 50:50 or 75:25 molar ratio and observed for up to 42 days or 70 days, respectively. Initial comedication with cyproterone acetate 1 mg/rat was injected SC once daily during the first 7 days post-implantation. Relative weight of the prostate and testes and relative binding capacity of pituitary LH-RH and testicular LH receptors were inhibited compared to untreated controls and testosterone secretion was suppressed for more than 42 and 70 days, respectively, for the two buserelin implants. At the end of the dose interval for the PLG 75:25 implants (day 56), the minimum release rate was

22.8 to 41.9 ug/day and 82 to 86% of the 3.3 mg dose was released by the implants. These implants degraded slowly with an accelerated period of disintegration starting on day 56 post-implantation (terminal $t_{1/2}$ was 20 days corresponding to the terminal phase of biodegradation).

HAMSTER
Following administration of 0, 2.5, 5.0, 25.0, or 50 ng/SC buserelin to male hamsters (and rats), the minimal effective dose for LH and FSH release in hamster was 2.5 ng (LH) and >50 ng (FSH). In rat the minimal effective dose was 2.5 ng for both variables.

GUINEA PIG
In guinea pigs, after a single dose of buserelin 100 ng/ 100 g bw/SC to males and females, peak LH levels occurred at 120 minutes post-dosing. Doses of 0, 4 or 16 mcg/kg buserelin/SC, to females for 28 days, followed by exposure to fertile males for 100 days during which drug treatment continued, resulted in 0% pregnancy rate in buserelin-dosed groups and 100% pregnancy rate in controls.

RABBITS
In adult male rabbits receiving daily subcutaneous injections of 0, 2, 20, or 200 mcg buserelin/kg body weight for 4 weeks, significant ($p<0.05$) reductions were observed in testes and prostate weight, pituitary LH, serum testosterone and testicular testosterone values, at high dose only. A reduction in hypothalamic LH-RH was not significant.
DOG
In male dogs, 2.5 mcg/kg/day/SC buserelin reduced serum testosterone levels to 6% of control. When buserelin was discontinued, after six months, testicular involution was reversible within two months.

In adult male Beagle dogs (n=12) treated SC with a single implant containing 3.3 mg buserelin acetate and PLG 75:25 or PLG 50:50, average duration of testosterone suppression with PLG 75:25 implants was 148-170 days whereas PLG 50:50 implants suppressed testosterone for 93-108 days. Serum testosterone returned to normal levels within 6 weeks after the end of suppression. A close relation between the minimum therapeutic release rate and maintenance of testosterone suppression was found. During the dose interval of 56 days, 72-75% and 90-96% of the dose were released from the PLG 75:25 and PLG 50:50 implants, respectively.

In a repeated dose study in male prepubertal dogs administered 3.3 mg buserelin implants of PLG 75:25 every 56 days for 392 days, serum testosterone was consistently suppressed to the prepubertal range during treatment until 129 days after the last implant injection. Thereafter, serum testosterone started to rise and sexual maturation was completed in all animals within 1 year and testicular histology was normal in all dogs within 2 years. The pharmacokinetics showed a reproducible release profile. The maximum release rate was found on the first day of implantation, the minimum therapeutic release rate was determined to be 13.8 ug/day and the terminal t1/2 of buserelin release from the implants was 26 days.

MONKEY
The effect of 5 mcg/day/SC/1 year buserelin was studied in nine female stumptail monkeys. Ovulation was inhibited in 3 of the animals. These animals became amenorrheic. Serum estradiol levels fluctuated between values associated with the early to mid-follicular phase of the normal cycle and never reached the late follicular phase. In a further 3 animals, buserelin also inhibited

ovulation, but serum estradiol levels occasionally rose to values associated with the late follicular phase, indicating that follicular maturation was not completely suppressed. These animals had irregular patterns of menstruation. In the remaining 3 animals, ovulation was not suppressed. Increasing the daily dose of buserelin to 20 mcg suppressed ovulation in 2 of these animals and reduced the number of cycles in the remaining one. Cycles in this last animal were suppressed when buserelin was administered at a dose of 10 mcg twice daily. At the end of dosing, almost all animals ovulated within 2-4 weeks.

In eight prepubertal male monkeys, each treated with 8 implants of PLG 75:25 followed by 11 implants of PLG 50:50, with 3.3 mg to 4.4 mg buserelin acetate per implant, every 4 weeks, testosterone (T) secretion remained suppressed in the prepubertal range during the entire treatment period until 70 days after the last implant. At this time, buserelin excretion in the urine had decreased below 1.5 ug buserelin/g creatinine. The minimum therapeutic release rate was determined to be 3.5 ug/day. After a recovery period of 12 months, serum T reached the adult range. Analysis of sperm counts, motility and morphology showed fully developed spermatogenesis in all monkeys.

ACROSS SPECIES

A comparison of acute equi-effective doses of buserelin and native LH-RH shows that the synthetic agonist was 42 times more potent in the **rabbit** follicle stimulation test, 120 times more potent in the **rat** LH release test, 100 times more potent in the **rat** ovary ascorbic acid test and 20 times more potent in the **sheep** LH release test.

PHARMACOKINETICS AND METABOLISM

Plasma elimination

Plasma elimination of buserelin was determined in two groups of 2 male rats (450-500 g) given 2 mcCi ^{125}I- buserelin/IV (2.15 ng buserelin) or 2 mcCi ^{125}I- buserelin plus an excess (50 ng) dose of unlabelled buserelin/IV in 2 mL saline. Continuous blood collection (500 mcg/5 min) preceded sacrifice at 90 minutes post-dosing. Plasma elimination followed a multi-exponential course with a rapid initial t1/2 = 10 min., an intermediate t1/2 = 26 min. and a prolonged t1/2 = 90 minutes. The excess buserelin dose did not change the plasma elimination rate.

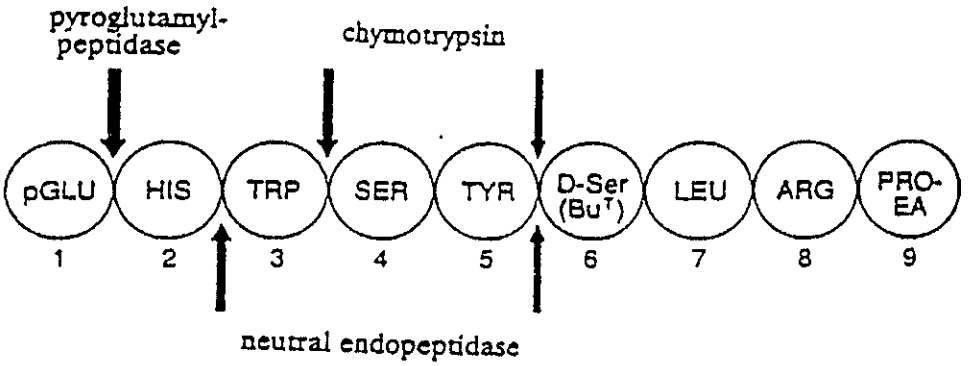
In further rat studies, buserelin 10 mcg/100 g bw/IV showed a physical t1/2 in plasma of 3-6 minutes using RIA methods. In the 60 minutes post-dosing (1 mcCi ^{125}I-buserelin) about 20% more buserelin was cleared compared to the same dose of labelled LH-RH.

Organ Distribution

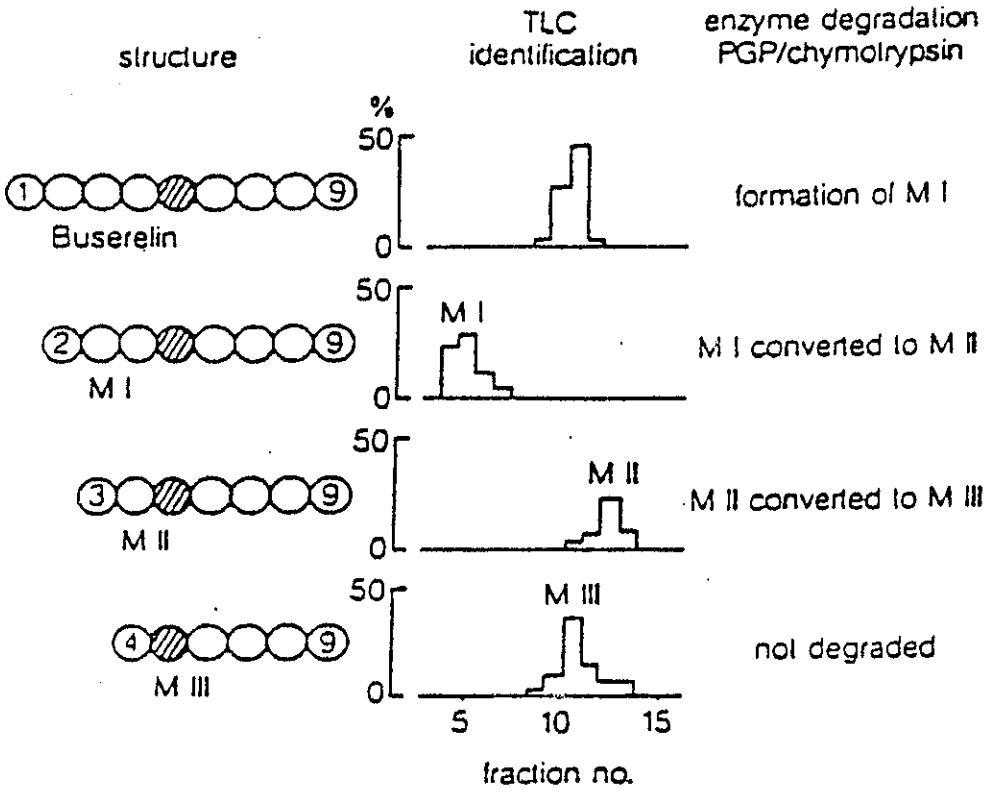
Two groups, each of 4 male rats, were given 1 mcCi of ^{125}I-buserelin (specific activity 200 mcCi/mg) or ^{125}I-LH-RH/IV and sacrificed 60 minutes post-dosing. Radioactivity was detected, in both groups, in liver, kidney, spleen, (skeletal) muscle and glands (adrenal, pituitary, thyroid, salivary). In terms of the percent of dose accumulated by tissue, liver (2.1% of LH-RH dose and 12.7% of buserelin dose) showed greatest accumulation followed by kidney (1.02% LH-RH dose and 5.5% buserelin dose). The pituitary (biological target organ for gonadotropin release) showed a much greater buserelin accumulation (0.035%) than LH-RH (0.0006%). The (3-9 heptapeptide) metabolite of buserelin does not accumulate in pituitary but is concentrated in liver and kidney.

Metabolism

The metabolism of buserelin was examined in rat and in-vitro by means of buserelin-^{125}I Tyr^5 which was biologically fully active. The metabolites were identified by TLC or HPLC or RIA. Immunological inactivation of buserelin is determined by N-terminal decomposition, by cleavage of the pyroglutamic acid- hesitating bond. Buserelin metabolism was examined in-vitro by inactivating unlabelled buserelin with enzyme preparation. Buserelin is rapidly inactivated by enzymes from liver, kidney and anterior pituitary. The main buserelin-degrading enzyme is pyroglutamyl-amino-peptidase (PGP), an enzyme which can be isolated from mammalian liver and anterior pituitary. Buserelin is also inactivated by chymotrypsin-like enzymes such as neutral endopeptidase from the pituitary.



Enzyme degradation of a nonapeptide agonist: Buserelin is inactivated by N-terminal degradation. Cleavage sites indicated by arrows. The Tyr^5-D-Ser(Bu^t)^6 bond is resistant to degradation. All C-terminal metabolites have negligible biological activity.



Identification of Buserelin metabolites in tissue extracts. (Left Panel) C-terminal Buserelin fragments of decreasing chain length, labeled in Tyr[5] with ^{125}I. (Middle panel) Chromatographic mobility on TLC plates (percent radio label per fraction). (Right panel) Products formed after sequential degradation with pyroglutamylaminopeptidase, followed by chymotrypsin.

Buserelin metabolites in the urine of the mouse, rat, dog, monkey and human administered buserelin SC in isotonic saline or buserelin implants were investigated (by HPLC/RIA) in one study to assess whether the metabolism in animal species was similar to that in human. Similar types of metabolites were detected in the urine of the mouse, rat, dog, monkey and human. The buserelin (5-9) pentapeptide was the main metabolite for all 5 species. The fraction of intact buserelin excreted in each species was different. None was found in the mouse and the highest amount (49.8% of total administered dose) was detected in the dog. The mouse had the highest and the dog had the lowest dose-requirement for testosterone (T) suppression. In the monkey and the human, there was a large fraction of intact buserelin in the urine (47.7% and 43.7%, respectively). The dose-requirement for suppression of oestradiol secretion in the female monkey and human (by infusion or implants) was similar. In the rat, the fraction of intact buserelin was lower (23%) than in the dog, monkey and human, and the dose required for half-maximal suppression of T secretion is higher than in the dog, monkey and human.

HUMAN PHARMACOLOGY

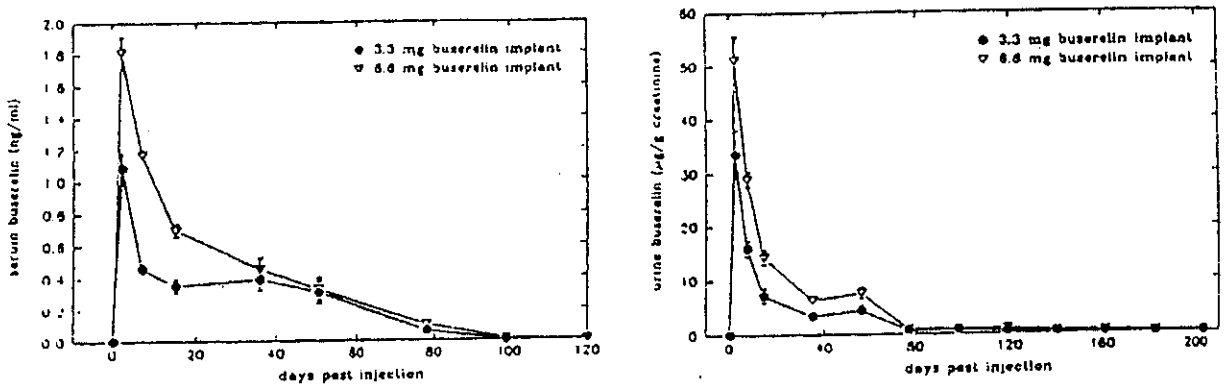
SUPREFACT® (buserelin acetate injection and nasal solution)

Three groups of healthy male subjects, aged 19-23, 33-44, and 45-60, were administered single IV injections of buserelin (1.25, 2.5, 5.0, 10.0, and 20 mcg) to assess dose-response by determination of LH and FSH levels (by RIA) in blood samples taken before and at injection, and at various times up to 24 hours after injection. Areas under the serum concentration time curves (AUC's) for each dosage indicated a positive dose-response for LH release in each age group, and a less pronounced dose-response for FSH. Times to peak responses were variable: for LH, 1/2 - 4 hours (no clear result in the 33-44 age group); for FSH, 1/2 - 8 hours. Generally, adverse effects were minor. In the 33-44 age group, among 49 total treatments (7 patients), adverse effects included: nightmares (1 patient each on buserelin and natural LH-RH; eosinophilia (1 patient, who also evidenced low neutrophil counts at the start and end of trial); normochrome anemia, considered as related to experimental (blood-letting) procedures.

In a dose-range finding study involving single intranasal (IN) dosages of 10, 25, 50, 100, 200, 500, 1250 or 2500 mcg of SUPREFACT®, 34 healthy males were selected: 24 participated once, 5 participated twice, and 5 participated 3 times (30 days between each treatment) for a total of 49 treatments. The observation period was 3 days pre-treatment (visits 1 to 3), day of treatment (visit 4), and for 6 days post-treatment (visits 5 to 10). Plasma hormone analysis (FSH, LH, prolactin, testosterone (T), dihydrotestosterone (DHT) , estradiol (E_2), pregnenolone and 17-OH progesterone) was performed for blood samples collected at visits 1, 2, and 4 to 10. Blood samples in the pre- and post-treatment phases were collected three times daily (8 am, 4 pm, 9 pm), and on the day of drug administration at -1/2, -1/4, 0, 1/2, 1, 2, 4, 6, 8, 12, and 14 hours relative to injection. Absolute mean hormone concentrations, mean percentage hormone values for each group, and 24-hour AUC's were determined. Generally, single IN SUPREFACT® doses over 500 mcg elicited maximal hormone responses: LH, FSH, 17-OH progesterone, DHT at 1250 mcg; T,E_2 at 2500 mcg. Duration of response was 24 hours. The principal response was by LH (increase); dose-dependent stimulation was seen for LH and estradiol and a slight tendency for dose-dependent stimulation was found for FSH, 17-OH progesterone, T, and DHT. No change was seen in pregnenolone. Single IN doses of SUPREFACT® leading to stimulation of LH and androgen hormone secretion caused a transient loss of diurnal cyclic variation and relatively low levels of plasma T and 17-OH progesterone lasting for one to three days of the post-treatment period. Clinical and laboratory profile was excellent; one volunteer complained of mild headache, nausea, and increased perspiration, not considered drug-related. Fluctuations in vital signs were not of clinical significance.

SUPREFACT® DEPOT 2 months (buserelin acetate implant)

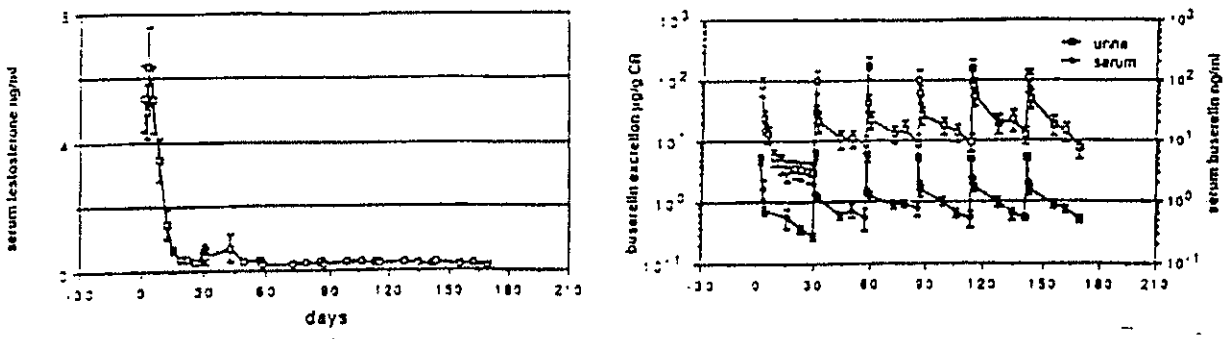
A single dose study was conducted in 16 healthy male subjects (mean age: 29.3 years; range: 21-35 years). The healthy volunteers were administered single injections of 3.3 mg (Group I, n=8) or 6.6 mg (Group 2, n=8) buserelin acetate implants, and 19-nortestosteronehexo-oxyphenylpropionate IM daily as comedication starting 7 days before the implant injection and once every 3 weeks up to week 23, to assess the pharmacokinetic profile of the implant by determination of immunoreactive buserelin levels in serum and urine (by RIA) at various time intervals.



Pharmacokinetic profile of a single injection of a 3.3 mg or 6.6 mg buserelin acetate implant dose. Linear graphs of serum buserelin versus time and urinary buserelin versus time (RIA method).

AUC values for the two doses were dose proportional. Mean residence times of buserelin after administration of 3.3 mg and 6.6 mg buserelin acetate implant were 4.7 ± 0.4 and 4.1 ± 0.3 weeks, respectively. At the end of 56 days, 82 and 84% of the 3.3 mg and 6.6 mg dose, respectively, had been released. No adverse events were reported. Deviations of laboratory values were considered minor and not related to study the drug.

In a multiple-dose pharmacokinetic study, 11 patients (mean age: 72 years; range: 55-81 years) with Stage B (n=4), C (n=6) or D2 (n=1) prostatic cancer were administered 3.3 mg buserelin acetate implants every 4 weeks for up to 6 months to assess the pharmacokinetics, efficacy and tolerance of the implants.

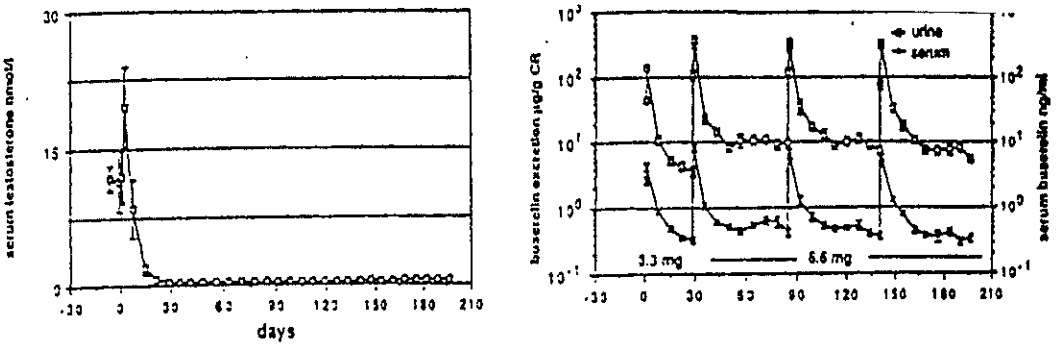


Graphical presentation of serum buserelin concentration, urinary buserelin excretion and serum testosterone concentration obtained after multiple administration of 3.3 mg buserelin implants, once every 4 weeks (RIA method).

All patients achieved surgical castration level (1.0 ng/mL) of serum T after 45 days which was maintained until the end of the study. According to National Prostatic Cancer Project (NPCP) criteria 3 of the 5 evaluable patients had no change in tumor status and 2 patients had partial remission (one of these had elevated prostatic acid phosphatase levels). No serious adverse events were observed. Seven patients experienced hot flushes, an expected side effect of hormonal castration.

The longterm effects of multiple administration of the 6.6 mg buserelin acetate implant on LH and testosterone (T) secretion were investigated in several studies. In one study, 28 patients (mean age: 73 years; range: 43-85 years, with Stage C (n=6) or D (n=22) prostatic cancer) initially received a 3.3 mg implant (23/28 cases as single dose; 4-week dosage interval) followed by 6.6 mg every 8 weeks (mean of 6 implants). All patients also received cyproterone acetate (150 mg/day [n=9] or 300 mg/day [n=9]) or flutamide (750 mg/day [n=10]) as initial antiandrogen treatment for flare reaction prophylaxis, given 7 days before the first implant and ending 28 days after the first implant. A local anaesthetic (Lignocaine 2%) was given to all patients prior to implant injection.

The serum and urinary buserelin and serum T and LH concentrations were assessed (by RIA) before and 4 hours after each implant as well as at weekly intervals for serum and urine buserelin.

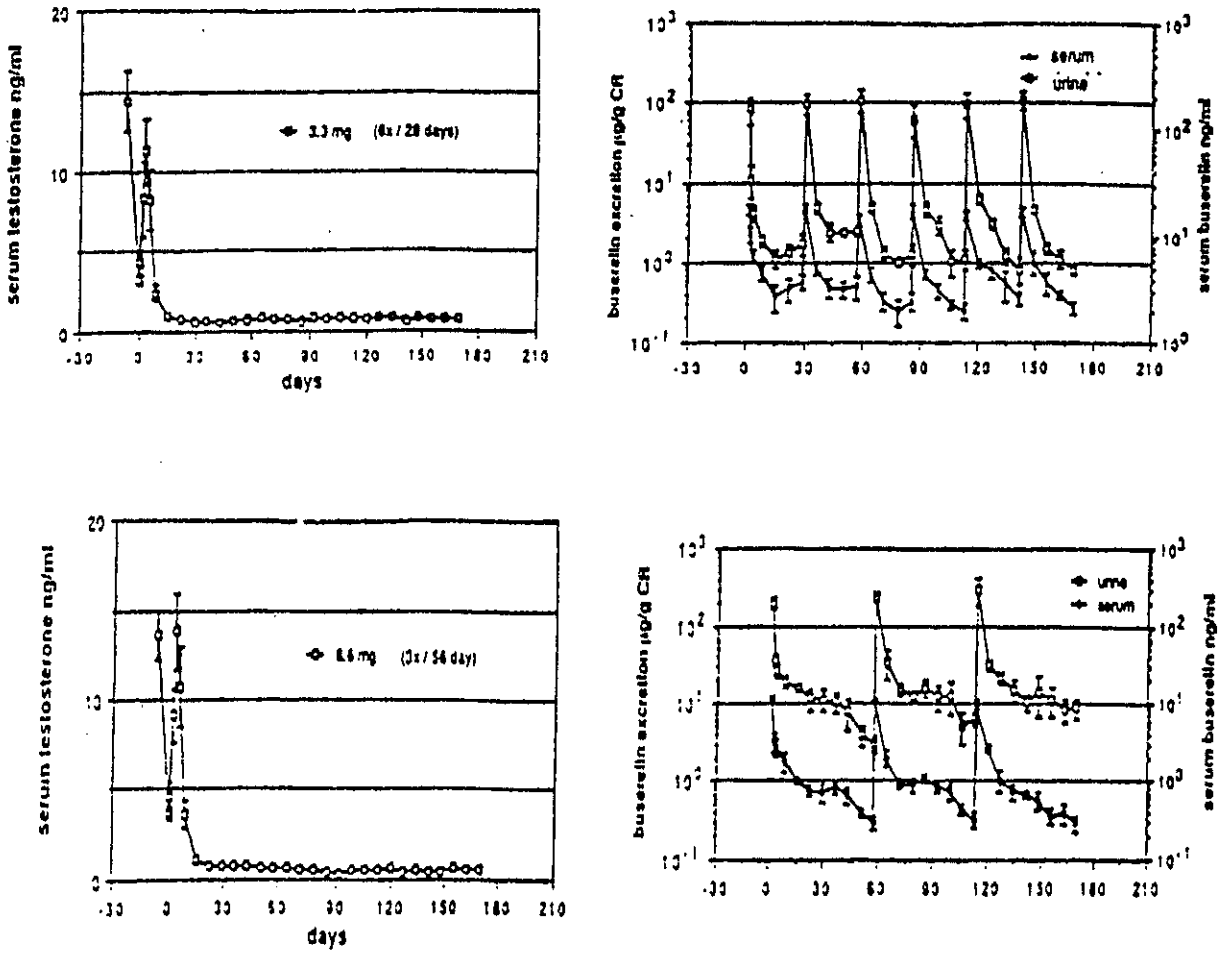


Graphical presentation of serum buserelin concentration, urinary buserelin excretion and serum testosterone concentration obtained after multiple administrations of 6.6 mg buserelin acetate implant following pretreatment with the 3.3 mg dose (RIA method).

There was a correlation between the therapeutic buserelin levels measured in the urine and serum and the suppression of T secretion. At trough levels (urinary excretion of 3.0 and 6.0 ug buserelin/g creatinine for the 3.3 mg and 6.6 mg dose, respectively), full T suppression was always maintained. No initial antiandrogen treatment was found superior on the basis of the study data. Local tolerance was good. Expected symptoms of androgen deprivation were reported. Laboratory investigations did not reveal any changes attributable to buserelin.

In a second study, 2 parallel groups received either 3.3 mg every 4 weeks (Group 1: 7 patients with Stage D1 or D2 prostatic cancer, mean age: 63; range: 60-81 years) or 6.6 mg every 8 weeks (Group 2: 7 patients with Stage D1 or D2, mean age: 67; range: 52-81 years).

All these patients also received initial comedication with an antiandrogen (cyproterone acetate 150 mg/day) starting one week before (Day -7) and ending 5 weeks after the first implant in order to avoid a clinical flare reaction. A third group in this study (Group 3: 3 patients with Stage C or D, mean age: 67; range: 60-79 years) was pretreated with buserelin nasal spray dose and did not receive an antiandrogen when starting buserelin implant treatment. If requested, a local anaesthetic (Lidocaine 1%) was given prior to implant injection.



Graphical presentation of serum buserelin concentration, urinary buserelin excretion and serum testosterone concentration obtained after multiple administration of 3.3 mg or 6.6 mg buserelin acetate implants to patients pretreated with an antiandrogen (Groups 1 and 2, respectively) (RIA method).

No stimulatory effect of the implant on LH and T secretion was found in Group 3 patients and none of these patients showed T values above castration levels at any time during the study. At C_{min} levels (urinary excretion of 6.0 and 4.4 ug buserelin/g creatinine for the 3.3 mg and 6.6 mg dose, respectively), full T suppression was always maintained in all patient groups. Local tolerance was good. Expected symptoms of androgen deprivation were reported. Laboratory investigations did not reveal any changes attributable to buserelin. One patient in Group 3 developed a severe headache 9 weeks after implant treatment initiation which continued about a year until the patient discontinued therapy. The causal relationship of headache with the study drug was judged highly probable.

TOXICOLOGY

Local Tolerance

Single-dose, local tolerance tests (IM/IV/IA/SC) of both buserelin injection (5 mcg/mL) and nasal solution (0.113% w/w) were conducted in each of 2 **rabbits**/ route of administration/dosage form. A volume of 0.1 mL (SC) or 0.5 mL (IV/IA/IM) was given. One of the two rabbits was sacrificed on day 1 (IV/IA) or day 2 (IM/SC) post-dosing and the remaining animal on day 2 (IV/IA) or day 5 (IM/SC) for histologic (macroscopic/microscopic) examination. Buserelin was tolerated by all routes.

Mucosal tolerance of SUPREFACT® (buserelin acetate) nasal solution (0.1 mL) in the **rabbit** (applied once to the conjunctival sac of the left eye of each of 6 animals with the right eye as control) was tested. Twenty-four hours later the eyes were rinsed with saline. There were no changes in the cornea, iris or conjunctiva attributable to drug.

Local tolerance of subcutaneous injection of SUPREFACT® DEPOT 2 months (buserelin acetate implant) was excellent in the repeated-dose studies in **monkeys** and in the carcinogenicity study in **rats**. No skin reactions or irritation were observed.

A single dose study in **rats** investigated the biodegradation and local tolerance of the implants. In 4-6 animals killed up to 10 weeks post-implantation, the tissue capsule surrounding the injection was assessed by scanning electron microscopy and showed a mild reaction with a thin fibrous texture and few multinucleated cells. Gradual swelling of the implant material was observed *in vitro* and in the rats until 8 weeks post- implantation, followed by accelerated degradation. After 3-4 months, implants had completely disappeared from the injection site.

Acute Toxicity

Mice, 10 males and 10 females, were given buserelin 0.5 mg/kg/IV and **rats,** 10 males and 10 females, were given 1 mg/kg/IV. There were no deaths and no abnormal findings.

Subacute and Chronic Toxicity

In **a 4-week** study, 4 groups of 10 male and 10 female initially immature **rats** were given 0, 0.05, 0.1 or 0.2 mg/kg/day/SC buserelin. Body weight gain was retarded in males and accelerated in females, testicular weight was reduced and there was a numerical preponderance of corpora lutea in ovaries. There were no adverse effects of buserelin on blood or urine parameters, or on histology at autopsy.

Eight groups of adult male **rats** were given buserelin, 0 or 200 ng/day/SC for 4, 6, 8 and **10 weeks**. Statistically significant reductions in weight of seminal vesicle (all weeks), and prostate gland and levator ani muscle (8, 10 weeks) were found, but no significant reductions in testicular weight. In-vitro testicular secretory capacity (for testosterone) was significantly reduced at all weeks.

In **a 6-month** study, 4 groups of 25 male and 25 female **rats** were given 0, 0.05, 2. 5 or 125 mcg/kg/day/SC buserelin. After 6 months, 5 animals per group were observed for a further 6 weeks without buserelin. At low dose, the ovaries showed a significant increase in corpora lutea and reduction in the intensity grade of tertiary follicles. Ovarian weight was increased. During the 6-week drug free observation period, the number of corpora lutea and the intensity grade of the tertiary follicles became normal. The mid-dose caused a prolonged oestrus cycle in the first,

second, fourth and fifth week. Ovaries behaved as in the low-dose group. The high dose caused an extension of the oestrus cycle at all observation periods. Ovarian histology was similar to that in the low dose group. At the end of the 26 test weeks a significant reduction in the ovarian weight and spermatocyst count were found. At the end of the 6-week observation period, ovarian weight and histology and spermatocysts were normal. There were no untoward effects on blood or urine parameters or organ histology at autopsy.

In these rats, at the end of 6 months' dosing, there were no consistent changes in levels of serum FSH, prolactin, GH or T_3. In males, serum LH levels were increased at low dose and significantly increased at mid-dose. No significant changes were observed in females. Pituitary LH content was significantly reduced in males at all dose levels but no changes were observed in females. Pituitary FSH showed no change in any sex/dose group. Pituitary content of LH was significantly decreased at all doses in male rats, and unchanged in female rats. Pituitary FSH, prolactin, GH and TSH were unchanged in male rats. Pituitary PRL, GH and TSH were decreased at the highest dose in female rats (due to reduced estrogen levels). Ovarian content of estradiol was slightly reduced at the highest dose, and progesterone content was increased at the two lower doses. Testicular testosterone content was unchanged in male rats in accordance with intact spermatogenesis. Adrenal corticosterone content showed no change in either sex at any dose.

In **a 14-day** nasal toxicity study in Beagle **dogs**, 2 male and 2 female animals received 100 mcg/day buserelin or the solvent (water) alone. The material was administered by atomizer to the left nostril. At autopsy, there were no pathological macroscopic or microscopic changes.

In **a 30-day** toxicity study in Beagle **dogs**, groups of 2 male and 2 female animals received 0, 0.05, 0.1 or 0.2 mg/kg/SC/day buserelin. There were severe disturbances in spermiogenesis and atrophy of the prostate gland in all treatment groups. Hematology, clinical chemistry, urinalysis and histology at autopsy did not show pathological changes.

In **a 6-month** toxicity study in Beagle **dogs**, 4 groups of 5 male and 5 female animals received 0, 0.05, 2.5 or 125 mcg/kg/SC/day buserelin. Thereafter, 2 animals per group and sex were observed for a further 8 weeks without buserelin. At the low dose, there was slight atrophy of the reproductive organs in 1 male and 2 females. After a further 8 weeks without dosing, there were no pathological changes. The mid and high dose caused a moderate to marked atrophy of the reproductive organs. The high dose led to atrophy of pituitary and thyroid glands. Behaviour, external appearance, hematology, clinical biochemistry, urinalysis and post-mortem examination of the organs did not indicate toxicity.

In male dogs, plasma LH and testosterone were markedly decreased after 6 months of treatment, plasma prolactin T_3 and T_4 were unchanged. In female dogs, plasma LH was also reduced, prolactin was unchanged, whereas T_3 was slightly increased at the lower doses, and T_4 was slightly increased at the highest dose. These changes are within normal functional variability. Plasma testosterone in male dogs was consistently suppressed from 1-6 months of treatment, values were normalized within 6 weeks after treatment. Plasma progesterone in female dogs indicated consistent reduction of luteal function from 3-6 months of treatment, with subsequent recovery during the post-treatment period. Estrous periods are infrequent in female dogs, and long lasting luteal phases were found in two animals (6 weeks duration), during the post treatment period in accordance with normal physiology. No antibodies against buserelin were detected in rats or dogs after 6 months treatment.

The treatment of ten juvenile (median age: 5 months) male Beagle **dogs** with 7 buserelin implants (dose 3.3 mg, dose interval of 56 days) resulted in an inhibition of sexual maturation during a treatment period of **17 months**, with an onset of puberty 5 months after the last implant injection. At this time, serum testosterone secretion started to rise, and 6-8 months after the last implant, adult testosterone secretion was present. Pituitary-testicular responsiveness to LH-RH was established when the buserelin release rate decreased below 0.75 ug/day. Testicular development and spermatogenesis proceeded normally to full maturation. Histological examination two years after the last implant injection showed normal spermatogenesis and normal pituitary tissue without indications of microadenoma.

The SC treatment of 8 juvenile (mean age: 3 years and 5 months) male Rhesus **monkeys** each with 8 implants of PLG 75:25 followed by 11 implants of PLG 50:50, dose of 3.3 mg to 4.4 mg buserelin acetate per implant, every 4 weeks, for a total treatment duration of **18 months** did not affect the health status of the animals. There was no morphologically detectable residual organ damage which could be attributed to the compound and there were no pituitary adenomas. At the implantation sites, no signs of local intolerance were observed. Histological examination of the testes, removed by hemi-castration at the end of the treatment period (about 5 weeks after the last implant) confirmed their juvenile state. At the end of the recovery period (47 weeks), the body weight development of the animals and the morphology of the remaining testis, prostates and seminal vesicles suggested a normal sexual maturation process. The testes showed fully developed spermatogenesis with no study-related residual damage. Oligospermia was only observed in one animal. Inhibition of sexual maturation by the buserelin implants was, therefore, fully reversible at the end of the recovery period (47 weeks).

Reproduction and Teratology

In a fertility study in **rat**, 4 groups of 30 male and 30 female animals received 0, 0.2, 0.5 or 1.8 mcg/kg/SC/day buserelin for 60 days (males) and 14 days (females) before mating. The dosing was continued until all animals were killed. Males and females of the same dosage group were mated. Half the females were killed on day 21 of pregnancy and the fetuses examined. The other half were allowed to litter and rear their offspring for 21 days. The surviving offspring (F_1 generation) were reared without buserelin dosing until maturity and mated. After parturition and 21 days of rearing the offspring (F_2 generation) the study was terminated. There was a dose-dependent weight reduction of testes, prostate and seminal vesicle in all dose groups. In the females, there were cycle disturbances in all dose groups. As dose increased, fertility decreased. There was no pregnancy in the high dose group. Pregnancy was prolonged, or birth was inhibited, in the two lower dose groups. There were no abnormalities in the fetuses of the animals killed after 21 days. The majority of the spontaneously born offspring were found dead. Only one litter was reared without complication. Function tests and mating attempts indicated no delayed compound toxicity.

In an embryotoxicity study in **rat**, four groups of 27 animals received 0, 0.4, 4 or 40 mcg/kg/day/IV buserelin from day 1 to 16 of pregnancy. On day 21 of pregnancy, the animals were killed. In all dose groups, ovarian weight was increased and large numbers of follicles and yellow bodies were found. Pregnancy was reduced in the mid and high dose groups. In the high dose group fetal mortality was increased. Fetuses showed slight developmental retardation such as poorer ossification at all dose levels, and decreased body weight and reduced length in the mid and high dose groups. In the mid and high dose groups, the placenta was enlarged. There was a dose-dependent enlargement of the renal pelvis in all 3 drug groups and in some cases the ureters were dilated.

In an embryotoxicity study in **rabbit**, four groups of 15 animals were given 0, 1, 10 or 100 mcg/kg/day/IV buserelin from day 1 to day 19 after mating. On day 29 after mating the animals were killed and delivered by cesarian section. Pregnancy did not occur in most of the mid-dose animals and in all of the high dose animals. In the observed fetuses, there were no abnormalities attributable to buserelin: 24 h post-delivery incubator viability was not impaired.

Carcinogenicity

Four groups (100 male and 100 female in control group, and 50 male and 50 female in each dose group) of Wistar **rats** were given 0, 0.2, 0.6 or 1.8 mcg/kg/day/SC buserelin in a physiological saline vehicle volume of 1 mL/kg, for 24 months (730 consecutive days). This dosing was followed by a 6 month, buserelin-free recovery period. Mid-dose males had some body weight gain retardation which occasionally reached statistical significance compared to controls and other dose groups. Dosed females showed a marked increase in body weight gain which reached statistical significance at 3 weeks into study and remained so during buserelin dosing. Mortality rate was greatest in low and mid-dose male groups and lowest in high-dose females. Reductions in testosterone and progesterone values were seen in all buserelin dose groups throughout the dose period. All dose groups showed testicular changes, namely tubular atrophy and Leydig cell hyperplasia, which were irreversible and, to some extent, dose-dependent. Females showed atrophy of the uterus. There was no indication of a compound-induced carcinogenic effect.

A study of 290 male and 290 female Wistar **rats** treated with buserelin implants or control every 56 days in the doses 0 (untreated control, n=100), 0 (placebo control: i.e., rods without drug substance, n=120), 0.825 mg (n=120), 1.65 mg (n=120) or 3.3 mg (n=120) of buserelin acetate per implant [approximately 25, 50 and 100 ug/kg/day] over a maximum period of 30 months (an interim killing took place after 12 months) revealed a treatment-related occurrence of adenomas of the anterior lobe of the pituitary gland (pars distalis) in almost all male and female rats of the three dose groups. These pituitary adenomas occurred at the same overall incidence for both sexes and across the dose groups. Compared to the corresponding spontaneous findings in both control animal groups, the pituitary adenomas occurred earlier and generally resulted in the animals' death, either directly or indirectly (moribund killing). Between the 35th and 50th week of study, the mortality rate in the buserelin treated male animals rose abruptly: 58%, 43% and 43% of the rats treated with 0.825 mg, 1.65 mg and 3.3 mg buserelin acetate implants, respectively, had died or had to be killed. At this time, only 7-10% of the treated female rats had dropped out of the study. The mortality rate in the females did not rise distinctly until the 64th week of the study. This sex-specific shift in the mortality rate prevailed until the end of the study. By the 107th week of the study, all buserelin treated rats of either sex had dropped out of the study. At this time, more than 75% of all control animals were still alive. No further treatment-related findings of other tumor types were detected. The mechanism of pituitary adenoma formation in rats is unknown. The finding can be considered as an irreversible toxic effect in rats treated at the selected high doses of buserelin acetate for more than six months.

Mutagenicity
In the Ames test in bacteria (Salmonella typhimurium and Escherichia coli), buserelin in doses of 0.8 to 2;500 mcg/ plate had no mutagenic activity.

Four groups of 5 male and 5 female NMRI mice were given 0, 0.5, 16.0 or 500 mcg/kg/buserelin SC in each of two doses spaced 24 hours apart. All animals were killed 6 hours after the last dose. From bone marrow specimens, and by count of polychromatic/normochromatic erythrocytes, no increase in erythrocytes with micronuclei was observed. Buserelin is not mutagenic by this test.

CLINICAL TRIALS

SUPREFACT® (buserelin acetate injection and nasal solution)

Overview:
The clinical efficacy and safety of SUPREFACT® in the treatment of patients with carcinoma of the prostate gland is based upon data collected in 20 studies on 835 patients drawn from 12 countries. NPCP criteria were employed in the evaluation (n = 775 patients). The patient population characteristics can be summarized as follows:

Disease Staging at Entry	**Number of Patients**
Stage A + B or not specified	22
Stage C	150
Stage D	663
TOTAL	835
SUPREFACT® Administration Route	
Intranasal	575
Subcutaneous	260
TOTAL	835
SUPREFACT® Dose	
As recommended	648
Maintenance dose only	56
SC/IN dose combination different to recommended dose	131
TOTAL	835

Stage D patients:
At entry to these studies, 663 patients had Stage D disease and 599 of these were included in clinical evaluation of disease status following treatment with SUPREFACT®:

Evaluation	Treatment	Duration	Total	
	<1 year	≥1 year	n	%
Missing evaluation/No data	60	4	64	9.7
Complete or partial regression	83	74	157	23.7
Stable	124	63	187	28.0
Progression and progression-suspected	176	79	255	38.5
Totals	443	220	663	100

North American Data Sub-set:
In a multicentre, open-label, non comparative study of SUPREFACT® treatment of patients with (American Urological System classification of Stage C or Stage D) carcinoma of the prostate gland, and in a comparison with National Prostatic Cancer Project (NPCP) Stage D2 patients as historic controls, 211 SUPREFACT® treated patients were entered with total patient distribution as follows:

PATIENTS	SUPREFACT®	DES (1)	ORCH (2)	TOTAL
Enrolled	211	3	35	249
Evaluation - Safety	207	3	34	244
- Efficacy **(3)**	185	3	33	221
Protocols (NPCP) #500/#1300				
Enrolled		133	70	203
Evaluation - Efficacy		120	59	179

(1) Diethylstilbestrol - oral dose of 1 mg q8h.
(2) (Surgical) orchiectomy.
(3) Of these 185 SUPREFACT®-treated patients available for evaluation of efficacy, 139 were Stage D2 patients: of these, 109 received SUPREFACT® treatment by continuous subcutaneous (SC) route while 30 patients received drug by SC route for first seven (7) days and intranasal route thereafter.

Efficacy

Objective Response:
The following Tables provide a capsule of major efficacy analyses:

Parameter	SUPREFACT®	DES/ORCH	DES
Early (<12 weeks) progression-free survival (%)	83.8±3.1	86.6±2.5	89.2±2.8
Mean progression-free survival (days)	488±70	589±68	605±70
2-year progression (%)	33.9±6.1	42.4±4.0	43.2±4.9
2-year life survival (%)	61.9±4.2	65.9±3.8	68.9±4.5

In a **best-objective-response analysis,** a subset of analysis of early progression-free survival (above) the patient distributions were:

Therapy	Progression	Stable	Regression		TOTALS
			Partial	Complete	
SUPREFACT®	23	56	59	4	142
DES/ORCH	24	89	46	20	179
DES	13	60	35	12	120

The rate of early progression-free survival in the SUPREFACT® group was not significantly different from the historic controls (combined) nor did the distributions in the subset (above) show any between-treatment-comparisons differences.

Long-term progression-free survival analysis showed no significant differences in the probability of progression-free survival in the SUPREFACT® group compared to either (NPCP) DES/ORCH or DES patients for up to 874 days of follow-up. Similarly, no differences were observed between patient survival (at 2 years follow-up) across groups.

Subjective Response: Pain (within SUPREFACT® comparison)
For the SUPREFACT® Stage D2 efficacy subjects, there was a significant improvement in pain category at all visits from Week 2 through Month 11. At all other visits, there was an improvement in pain category that did not achieve statistical significance.

Endocrine Evaluation:
In terms of testosterone suppression, mean serum testosterone values rose slightly at Week 1, then fell at each succeeding visit for the first 4 months to a value of less than 40 ng/dl. From Month 4 through Month 24, mean serum testosterone values were essentially constant, fluctuating at 30-40 ng/dl. The median time required to suppress testosterone to castration levels (<100 ng/dl) was three weeks for either route of administration.

Safety

In terms of drug safety, two patients are described as experiencing clinical "flare" of metastatic prostate carcinoma disease early in SUPREFACT® treatment (both patients taking SC drug). One patient was withdrawn from buserelin treatment and was treated surgically. The other continued SUPREFACT® (reduced dosage - end of Week 1) treatment and submitted to radiation therapy to spinal metastatic deposits: his SUPREFACT® treatment was not interrupted.

Other safety data (NPCP patients excepted) distributions are as follows:

	SUPREFACT®	
	Subcutaneous	**Intranasal**
Hot flushes	71.6%	66.1%
Loss of libido (1)	84.8%	75.0%
Impotence (1)	79.4%	75.0%
Nasal irritation (2)		12.5%
Headache (2)		28.6%

(1) Over 50% of patients enrolled reported loss of libido.
(2) Not all of these cases were considered (by investigators) to be drug related.

Other side effects considered SUPREFACT® related were:
-Gynaecomastia (n = 4 or 2.6%)
-Pruritus (n = 2 or 1.3%)
-Gastrointestinal disturbance (n = 5 or 3.0%)

SUPREFACT® DEPOT 2 months (buserelin acetate implant)

An open-label, non-comparative international multicentre study was conducted to investigate the endocrine and clinical efficacy and the safety of SUPREFACT® DEPOT 2 months in the treatment of patients with Stage D carcinoma of the prostate gland. 301 patients who had not received previous systemic therapy were enrolled in 16 countries for treatment up to 5 years. An interim analysis was carried out on 241 patients treated for up to 1 year from 29 centres in 10 countries. All patients received SUPREFACT® DEPOT 2 months (6.6 mg buserelin acetate per implant) every 2 months and all but three patients received concomitant antiandrogen treatment (cyproterone acetate 150 mg/day) as flare-up prophylaxis for the first five weeks starting 7 days prior to the first implant injection. NPCP criteria were employed in the evaluation of 70% of the patients; 25% of patients were assessed with EORTC and 5% with ECOG criteria. The patient population characteristics can be summarized as follows:

Number of Patients	**Disease Staging at Entry***			
	C1	**C2**	**D1**	**D2**
Evaluable for efficacy	-	-	30	200
Evaluable for safety only**	3	2	1	5
Total number for each stage (% of total sample [n=241])	3 (1.2)	2 (0.8)	31 (12.9)	205 (85.1)

* *Assessment according to the American Urology Association classification system*

** *11 patients not evaluated for efficacy: 7 failed to comply with the inclusion criteria (5 Stage C cancer; 1 with a second primary neoplasm; 1 with clinical condition worse than PS3) and 4 patients failed to comply with protocol by receiving additional antitumour treatment.*

The efficacy and safety data obtained from the clinical studies with the buserelin implant were compared to historical control data which included the non-implant patients mentioned above (see SUPREFACT® - North American subset analyses) as well as patients from additional international studies treated with SUPREFACT® injection and nasal solution. Although the non-implant studies were carried out over an extended period of time, with variations in study design, the treatment groups were nevertheless very similar with regard to the primary disorder. 1522 patients treated with the non-implant formulations were evaluated for safety; 1422 of these were assessed for efficacy as well (967 patients with Stage D2 prostatic carcinoma). Patients evaluated for efficacy were treated for a median of 14 months: 76% of these patients were treated IN with 400 ug/300 ug t.i.d.; 20% treated SC with 200 ug daily; and 3% with combination therapy (IN/SC).

Efficacy

Objective Response:

The following Tables provide a capsule of major efficacy analyses in patients treated with SUPREFACT® DEPOT 2 months (6.6 mg buserelin acetate per implant) as well as an initial antiandrogen comedication (cyproterone acetate 150 mg/day for the first 5 weeks starting 7 days before the first implant injection):

Best-objective-response analysis

Evaluation	Stage D1 [n (%)]	Stage D2 [n (%)]
summary over all criteria (NPCP, EORTC and ECOG)		
stable (or better) progression not assessable	29 (97%) 1 (3%) -	178 (89%) 17 (9%) 5 (3%)
number of patients	*30 (100%)*	*200 (100%)*

Survival Analysis (Kaplan and Meier Rate Estimators), Stage D2 Patients*

Interval	Rate Estimate
Progression Free Survival Time	
0-3 months	97.9%
0-6 months	87.2%
0-9 months	76.8%
0-12 months	64.1%
Cumulative Survival Time	
0-3 months	95.4%
0-6 months	92.8%
0-9 months	87.2%
0-12 months	79.3%

* *Due to the small sample number in Stage D1, survival statistics were not calculated.*

The estimated progression-free survival time and estimated cumulative survival time after one year of treatment in 967 Stage D2 prostate cancer patients of the historical controls (patients treated with buserelin acetate injection and/or nasal solution) was 60.7% and 77.8%, respectively, which is comparable to the data from 6.6 mg buserelin acetate implant therapy.

Subjective Response: Pain, Impaired Performance and Urinary Outflow Disturbances
For the Stage D1 and D2 efficacy patients, symptoms such as pain, impaired performance and urinary outflow disturbances improved in the first four months. Median phosphatase levels returned to normal in the same period.

Endocrine Evaluation:
Luteinizing hormone median values dropped to low levels within the first two months. Almost all (99%) of testosterone values dropped into the castration range within 6 weeks. No signs of intercurrent stimulation of LH or testosterone after repeated administration of the 6.6 mg buserelin acetate implant.

Escapes (patients with testosterone levels above surgical castration levels during SUPREFACT® DEPOT 2 months treatment) were observed in 1.6% (33/2315) of all determinations in 14/29 centres in 3 countries in the implant studies. In comparison, non-implant data with the intranasal and daily subcutaneous buserelin formulations showed that 10.6% (100/939) and 2.4% (27/1104) of all testosterone determinations were above the castration range after 6 weeks of therapy.

Safety

Local Tolerance: Regardless of whether the implant was administered with or without local anaesthesia, the patients assessed tolerance as good and fair in 98.6% and 1.4% of all evaluated implantations, respectively.

Buserelin Antibody Titration: No antibody formation to buserelin or natural LH-RH was detectable after 12 months of treatment in the 82 patients tested.

Adverse Events: All 241 patients were included in the safety evaluation. 167 of the 174 patients treated for 1 year had complete documentation for the year. Adverse reactions were reported for 29% of patients and almost all occurred for the first time in the first 6 months of treatment (23% of all patients). Most were caused by hormone deprivation.

The main body systems involved were the central nervous system (19.1% of patients), cardiovascular system (5.8%), skin and appendages (3.3%) and urogenital system (2.1%). The most frequent adverse reactions are as follows:

Hot flushes	15.8% (n=38)
Loss of libido	2.5% (n= 6)
Impotence	1.2% (n= 3)
Injection site pain	1.2% (n= 3)

Other side effects considered to be remotely, possibly or probably related to SUPREFACT® DEPOT 2 months and occurring in more than 1% of patients were:

- Blood pressure increase: hypertensive crises in the presence of known hypertension (1.7% of all patients) and newly-diagnosed hypertension (2.5% of all patients) were both documented.

- The incidence of depression (2.9%), including suicide in 1 patient, fell into the range known for tumor patients. A causal relationship with the androgen deprivation caused by buserelin cannot be ruled out, but seems unlikely.

- Mild, transient oedema of the calves was seen in 2.1% of patients.

Loss of diabetic control was causally related to treatment and was seen in 2/241 patients (0.8%). Despite initial concomitant antiandrogen administration, symptoms in 0.8% of patients deteriorated at the start of buserelin therapy. The symptoms were not severe and resolved rapidly as treatment progressed.

Laboratory Investigations: No trends were observed. Changes in levels were related to underlying diseases. The medians of the alkaline phosphatase (AP) and total acid phosphatase (TAP) were always normal (changes of 122 to 142 U/l for AP and 10.2 to 9.5 U/l for TAP) during the 12 months. Prostatic acid phosphatase fell from 4.3 U/l to 1.2 U/l in the normal range.

A similar safety profile was observed for the non-implant formulations (injection and nasal solution) and other LH-RH agonists.

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