PRODUCT MONOGRAPH

PrSUPREFACT® DEPOT 2 months

Buserelin acetate implant
buserelin base 6.3 mg

and

PrSUPREFACT® DEPOT 3 months

Buserelin acetate implant
buserelin base 9.45 mg

Luteinizing Hormone-Releasing Hormone (LH-RH) Analogue

CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489 Greifswald
Germany

Date of Revision: June 3, 2020

Distributed by
Xediton Pharmaceuticals Inc.
2000 Argentia Rd, Mississauga
Ontario L5N 1W1
Tel: 1-888-XEDITON

Submission Control No.: 237855

PRODUCT MONOGRAPH

PrSUPREFACT® DEPOT 2 months
Buserelin acetate implant
buserelin base 6.3 mg

and

PrSUPREFACT® DEPOT 3 months
Buserelin acetate implant
buserelin base 9.45 mg

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 persists 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 equivalent to 6.3 mg of buserelin base), 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 2 months 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.

Similarly the release profile of SUPREFACT DEPOT 3 months (buserelin acetate implant equivalent to 9.45 mg of buserelin base) is biphasic; the initial release (T_{max} < 1day) is followed by a phase with slow, steady release lasting more than the 3-month dosing interval. A second small increase in the serum buserelin concentration was detected between weeks 12 and 16. At 16 weeks, median serum levels of buserelin were far above the detection limit (0.05 ng/mL), indicating considerable release reserve, and testosterone levels were in the surgical castration range. Sixteen weeks after single-dose administration of SUPREFACT DEPOT 3 months (buserelin acetate implant equivalent to 9.45 mg of buserelin base), urinary excretion of buserelin is between 2 and 31 µg/g creatinine (estimated threshold for suppression of testosterone secretion is 1 µg/g creatinine). This indicates that the release characteristics of buserelin from the implant ensure therapeutically effective systemic concentrations for at least 3 weeks after the end of the proposed dosing interval (3 months).

INDICATIONS AND CLINICAL USE

SUPREFACT DEPOT 2 months and SUPREFACT DEPOT 3 months are indicated for the palliative treatment of patients with hormone-dependent advanced carcinoma of the prostate gland (Stage D).

CONTRAINDICATIONS

SUPREFACT DEPOT 2 months and SUPREFACT DEPOT 3 months 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).

SERIOUS WARNINGS AND PRECAUTIONS

SUPREFACT DEPOT 2 months and SUPREFACT DEPOT 3 months should be prescribed by a qualified physician experienced in the use of hormonal therapy in prostate cancer.

SUPREFACT DEPOT 2 months and SUPREFACT DEPOT 3 months should be administered by a healthcare professional (see DOSAGE AND ADMINISTRATION section).

The following are clinically significant adverse events

- Clinical testosterone flare reaction in men with prostate cancer (see General section below, PRECAUTIONS and ADVERSE REACTIONS sections)
- Osteoporosis (see PRECAUTIONS section)

WARNINGS

General

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

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 (buserelin acetate implant) and SUPREFACT DEPOT 3 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.

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

General

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 2 months and SUPREFACT DEPOT 3 months, 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).

No studies on the effects on the ability to drive and use machines have been performed. 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). Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

Cardiovascular

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

There may be a relationship between androgen deprivation therapy and cardiovascular risk in men with prostate cancer on the basis of the demonstrated adverse impact of androgen deprivation on traditional cardiovascular risk factors, including serum lipoproteins, insulin sensitivity, and obesity (see References section).

Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential cardiovascular risk.

Androgen deprivation therapy has the potential to prolong QT/QTc interval on ECG. Physicians should also consider whether the benefits of androgen deprivation therapy outweigh the potential risk in patients with electrolyte abnormalities or congestive heart failure and in patients taking Class IA (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medications. (See PRECAUTIONS, Drug interactions)

SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months should not be administered to patients with congenital long QT syndrome, and should be discontinued in patients that develop QT prolongation during treatment.

Assessment of cardiovascular risk and management according to local clinical practice and guidelines should be considered.

Endocrine and Metabolism

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

Reduction in glucose tolerance

A reduction in glucose tolerance and an increase in diabetic risk have been observed in men treated with androgen deprivation therapy through orchiectomy or a LHRH agonist.

Therefore, diabetic patients and other patients at risk may require more frequent monitoring of blood glucose when receiving androgen deprivation therapy.

Hematologic

Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered.

Immune

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 2 months or SUPREFACT DEPOT 3 months, it may be necessary to surgically remove the implant.

Muscoloskeletal

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. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered during androgen deprivation therapy.

Psychiatric

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

Monitoring of patients:

Regular clinical assessment of patients and appropriate laboratory tests are recommended.

The response to treatment may be monitored by measuring serum testosterone, prostatic acid phosphatase (PAP) 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.

It is recommended that blood pressure be monitored regularly in patients with hypertension (See PRECAUTIONS, Cardiovascular).

Glycemic control tests such as blood glucose levels should be performed regularly in diabetic

patients (See PRECAUTIONS, Endocrine and Metabolism).

Evaluation of blood glucose levels may be undertaken at baseline and periodically thereafter for patients at risk.

Evaluation for QT prolongation should be undertaken for patients at risk by baseline ECG recording and frequently during treatment in patients also taking medicinal products known to prolong the QTc interval or to induce torsades de pointes (See PRECAUTIONS, Cardiovascular and PRECAUTIONS, Drug interactions). As electrolyte abnormalities may prolong the QT interval, baseline measurements of serum electrolytes, including potassium, calcium, and magnesium levels, should be considered.

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].

Co-administration of androgen deprivation therapy with medicinal products known to prolong the QTc interval or to induce torsades de pointes should be carefully evaluated. Such medicinal products include but are not limited to the examples that follow: Class IA (e.g. quinidine, disopyramide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine), antidepressants (e.g. amitriptyline, nortriptyline), opioids (e.g. methadone), macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g. moxifloxacin), pentamidine, antimalarials (e.g. quinine), azole antifungals, 5-hydroxytryptamine (5-HT3) receptor antagonists (e.g. ondansetron), and beta-2 adrenoceptor agonists (e.g. salbutamol).

In case of SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months treatment in combination with such medicinal products, the QT interval should be closely monitored.

ADVERSE REACTIONS

The adverse effects observed in patients treated with SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months 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 and PRECAUTIONS].

In patients treated with SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months, 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.

Very rare cases of pituitary adenomas were reported during treatment with LH-RH agonists including buserelin.
SUPREFACT DEPOT 2 months and SUPREFACT DEPOT 3 months

No serious clinical flare reactions were reported in patients (n=379) enrolled in clinical studies with SUPREFACT DEPOT 2 months and SUPREFACT DEPOT 3 months.

The following table provides a listing of adverse reactions, incidence ≥1%, considered to be at least possibly or probably related to buserelin acetate implant during a 5 year study with SUPREFACT DEPOT 2 months and a single dose, 16 week study with SUPREFACT DEPOT 3 months. Both studies were non-comparative, open label studies.

Listing of Adverse Reactions (at least possibly or probably related), Incidence ≥1%

Adverse Event	SUPREFACT DEPOT 2 months (buserelin acetate implant equivalent to 6.3 mg of buserelin base) Multidose 5 year study N=299		SUPREFACT DEPOT 3 months (buserelin acetate implant equivalent to 9.45 mg of buserelin base)* Single dose 16 week study N=22		
			cyproterone acetate + Buserelin		Buserelin (> 1 week after cyproterone acetate intake**)
	n	%	n	%	n %

Adverse Event	SUPREFACT DEPOT 2 months (buserelin acetate implant equivalent to 6.3 mg of buserelin base)		SUPREFACT DEPOT 3 months (buserelin acetate implant equivalent to 9.45 mg of buserelin base)* Single dose 16 week study N=22			
Hot flashes	47	15.7	5	22.7	3	13.6
Libido decrease	7	2.3	--	--	1	4.5
Hypertension	6	2.0	2	9.1	1	4.5
Depression	6	2.0	--	--	--	--
Pain	5	1.7	--	--	--	--
Impotence	5	1.7	5	22.7	2	9.1
Injection Site Reaction	4	1.3	1	4.5	--	--
Edema	3	1.0	--	--	--	--
Asthenia		< 1.0%	3	13.6	3	13.6
Myalgia		--	1	4.5	1	4.5
Arthralgia		--	--	--	1	4.5
Increased appetite		--	--	--	1	4.5
Insomnia		< 1.0%	1	4.5	--	--
Nausea		--	1	4.5	--	--
Palpitation		--	1	4.5	--	--
Dizziness		--	1	4.5	--	--

-- Not detected as at least possibly or probably related
* Cyproterone acetate given from 1 week before until 4 weeks after buserelin injection.
** > 1 week after discontinuation of cyproterone acetate

Other adverse reactions, arranged by body system, and, at least possibly or probably related to the administration of SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months (individual signs/symptoms occurred at an incidence of less than 1%) were:

Body as a whole: Non-serious clinical flare reaction, asthenia, fever
Cardiovascular system: Heart failure, tachycardia, thrombophelebitis
Digestive system: Constipation, fecal incontinence, nausea
Endocrine system: Exacerbation of pre-existing diabetes mellitus, hyperglycaemia
Musculoskeletal system: muscle cramps, myopathy
Metabolic and nutritional disorders: Weight gain, weight loss
Nervous system: Hyperalgesia, nervousness, sleep disorder (insomnia), suicide attempt, sweating increased
Respiratory system: Dyspnea, pharyngitis
Skin and appendages: Gynaecomastia, injection site haemorrhage, pruritus, rash
Special senses: Blindness in one eye (temporary)
Urogenital system: Abnormal ejaculation, male genital pain, urogenital disorder
Haemic and Lymphatic: Myeloid metaplasia

Arthritis, eye disorder, eczema, headaches, thrombosis and palpitations have been reported as remotely related to the administration of SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months.

MISCELLANEOUS

In the literature and in our 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):

Cardiac disorders: QT prolongation
Digestive system: Changes in appetite (e.g. anorexia), increased thirst, vomiting
Endocrine disorder: atrophy of the testes
Haemic and lymphatic system: Leukopenia, thrombopenia
Laboratory values: Changes in blood lipids (e.g. hypercholesterolemia, hyperlipidemia), increase in bilirubin levels, increase in serum liver enzymes levels (e.g. transaminases)
Musculoskeletal system: The use of LHRH-agonists may be associated with musculoskeletal discomfort and pain (including shoulder pain/stiffness in women). It 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.
Nervous system: Concentration and memory disturbances, dizziness, drowsiness, emotional instability, feelings of anxiety, mood changes, nervousness, tiredness
Skin and appendages: Articular pains, rhinorrhea, skin reaction (wheal) allergy, changes in scalp and body hair (increase or decrease)
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 DEPOT 2 months or SUPREFACT DEPOT 3 months.

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

SUPREFACT DEPOT 2 months and SUPREFACT DEPOT 3 months is intended for the long-term treatment of prostatic carcinoma. SUPREFACT DEPOT 2 months and SUPREFACT

DEPOT 3 months should be administered at approximately equal time intervals to ensure that the desired therapeutic effect is maintained.

The applicator containing the implant rods should be kept horizontal before injection [See INSTRUCTIONS FOR USE]. Before injection, a local anaesthetic may be used if desired.

SUPREFACT DEPOT 2 months (buserelin acetate implant)
The contents of one applicator, consisting of two implant rods, equivalent to a total of 6.3 mg buserelin base is injected subcutaneously every two months into the lateral abdominal wall. 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.

SUPREFACT DEPOT 3 months (buserelin acetate implant)
The contents of one applicator, consisting of three implant rods, equivalent to a total of 9.45 mg buserelin base is injected subcutaneously every three months into the lateral abdominal wall. It is important to maintain a regular, three-month rhythm for the dosage interval. In exceptional cases, the dosage interval may be shortened or extended by a few days.

Initial antiandrogen comedication:
About seven days before the first injection of SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 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 or SUPREFACT DEPOT 3 months injection, when testosterone levels can be expected to have entered the surgical castration range.

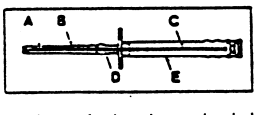
INSTRUCTIONS FOR USE

SUPREFACT DEPOT 2 months (buserelin acetate implant)
and
SUPREFACT DEPOT 3 months (buserelin acetate implant)

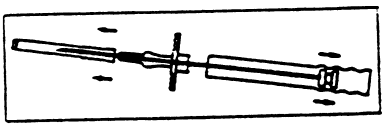
INSTRUCTIONS FOR USING THE APPLICATOR

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.

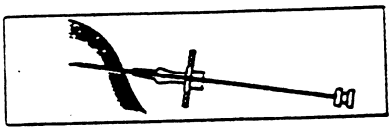
1. After removing the applicator from the foil wrapping, check that the implant rods are located in the window of the handle. If necessary, tap the protective cap of the needle lightly to reposition them in the window.



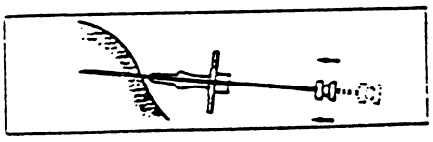
2. Disinfect the injection site of the lateral abdominal wall and administer a local anaesthetic, if desired. After removing the protective case from the plunger (E), remove the cap from the injection needle (B).



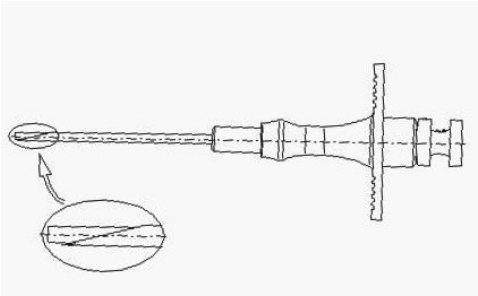
3. Lift a fold of skin and insert the needle approximately 3 cm (somewhat more than 1 inch) into the subcutaneous tissue, with the tip of the needle pointed slightly upwards. Withdraw the applicator about 1 to 2 cm prior to injection of the implant rods.



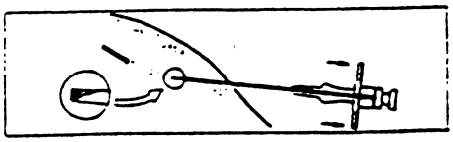
4. While fully depressing the plunger, inject the implant rods into the subcutaneous tissue. Compress the puncture channel while withdrawing the needle so that the implant rods are retained in the tissue.



5. When the plunger is completely inserted to its final position (plunger knob is touching the body of applicator), the front end of the plunger protrudes the top of the cannula, protecting the needle and minimizing the risks of needle stick injuries.



6. To ensure that the 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)

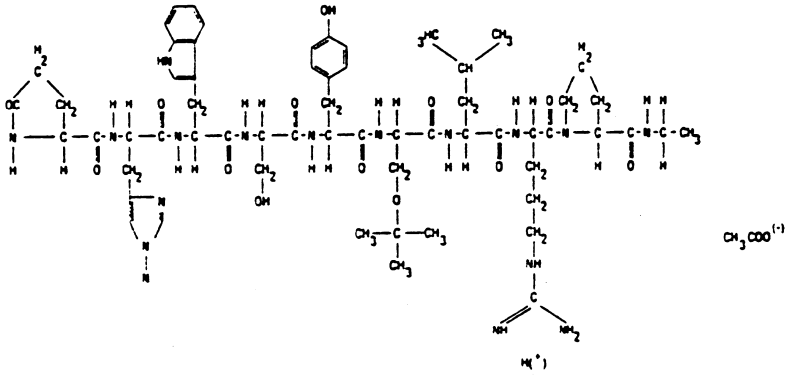
Chemical name:

5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O-tert*-butyl-D-seryl-L-leucyl-L arginyl-L-proline-ethylamide-acetate

or

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

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:

SUPREFACT DEPOT 2 months (buserelin acetate implant)
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.

SUPREFACT DEPOT 3 months (buserelin acetate implant)
Each applicator contains one implant dose consisting of three identical cream-coloured, biodegradable and biocompatible rods. Each implant dose contains a total of 9.9 mg buserelin acetate, equivalent to 9.45 mg buserelin base, and 39.4 mg poly-(D,L-lactide-co-glycolide) in a 75:25 molar ratio.

STABILITY AND STORAGE RECOMMENDATIONS:

Store the intact package between 15°C-30°C. PROTECT FROM EXCESSIVE HEAT and do not use beyond the expiration date printed on the container label.

AVAILABILITY OF DOSAGE FORMS:

SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months is packaged in a sterile ready-to-use disposable applicator with an integrated safety engineered 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 SUPREFACT DEPOT 2 months consists of two identical rods, while SUPREFACT DEPOT 3 months consists of three identical rods.

INFORMATION FOR THE PATIENT

KEEP MEDICINES OUT OF REACH OF CHILDREN.

SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months 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 DEPOT 2 months or SUPREFACT DEPOT 3 months is a drug containing buserelin in a white-cream coloured cylindrical rod-shaped implants. **SUPREFACT DEPOT 2 months (buserelin acetate implant) or SUPREFACT DEPOT 3 months should be kept between 15°C-30°C in the original container. Do not expose to excessive heat. Do not use SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months beyond the expiry date printed on the label.**

SUPREFACT DEPOT 2 months is administered to you by your doctor or a health care professional once every two months. SUPREFACT DEPOT 3 months is administered every three months. 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.

If you suspect a drug overdose, immediately see your doctor, go to your nearest hospital emergency department or contact a regional Poison Control Centre immediately. Do this even if there are no signs of discomfort or poisoning.

SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 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 worsening disease process such as pain (e.g. shoulder pain/stiffness, back pain, pain in the limbs and joint discomfort), or increased pain, or increased difficulty urinating. Should you experience events such as these, contact your doctor without delay.

As for other products of its class, buserelin therapy may lead to development of osteoporosis and an increased risk of bone fracture. The risk of skeletal fracture increases with the duration of therapy.

The reduction in testosterone associated with your treatment may have negative impact on some risk factors associated with heart disease. Your doctor will determine your risk and will assess your medical condition appropriately. Tell a doctor or pharmacist if you feel a very fast, uneven or forceful heartbeat (palpitations), shortness of breath, chest discomfort, or if you feel faint during treatment with SUPREFACT DEPOT.

SUPREFACT DEPOT may cause dizziness. Do not drive a car or operate machinery until you know how the drug affects you.

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.

An increase or decrease in scalp and body hair may also be observed with buserelin treatment.

Very rare cases of benign tumor of the pituitary gland (i.e. small pea size gland located at the base of the brain) were reported during treatment with buserelin, as for other products of its class.

In isolated cases, anaphylactic/ anaphylactoid shock (i.e. extreme allergic reaction) have been observed in patients treated with buserelin.

The reduction in testosterone associated with your treatment may reduce your number of red blood cells. Your doctor will do the appropriate monitoring.

The effect of antidiabetic drugs may be reduced during treatment with buserelin. If you are a diabetic patient, your doctor will check your blood sugar levels regularly.

Drugs that may interact with SUPREFACT DEPOT and may cause a change in heart rhythm (QT prolongation) include, but are not limited to:
- antiarrhythmic drugs (used to treat abnormal heart rhythm) such as: quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, dronedarone, flecainide, propafenone
- antipsychotic drugs (used to treat mental disorders) such as: chlorpromazine
- antidepressant drugs (used to treat depression) such as: amitryptiline, nortryptiline
- opioid drugs, such as: methadone
- antibiotics, such as: erythromycin, clarithromycin, azithromycin, moxifloxacin
- antimalarials, such as: quinine
- drugs belonging to a class called 5-HT3 antagonists, such as: ondansetron.
- drugs belonging to a class called beta-2 agonists, such as: salbutamol

Your doctor will be able to advise you what to do if you are taking any of these medicines. Your doctor may also perform some blood tests.

Talk to your doctor or pharmacist if you take any other medications or before using over-the-counter medicines or herbal products. Your doctor or pharmacist will evaluate the risk

of interaction with this medication.

Do not make any changes in your treatment program without first discussing the intended change with your doctor. If you forget to have SUPREFACT DEPOT 2 months or SUPREFACT DEPOT 3 months administered on the specified day, 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 µg/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 $t_{o/2}$ was 20 days corresponding to the terminal phase of biodegradation).

Adult rats (n=18) were administered a single dose implant containing 3.3 mg buserelin acetate and then observed for 112 days. The implant has sufficient release rate to suppress testosterone for more than 3 months; the release rate was >5 µg/day at day 112. In rats (n=16) implanted with 6.6 mg (2 rods) buserelin acetate and then observed for 112 days, size and weight of implants decreased from day 84 onwards. The residual buserelin content decreased time-dependently from week 2 until week 16 (74.31% of initial content versus 3.3% of initial content).

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 µg/day and the terminal $t_{1/2}$ of buserelin release from the implants was 26 days.

In Labrador dogs (n=4) treated with a single 3.3 mg dose of buserelin implant and observed for 246 days, serum testosterone was suppressed for an average duration of 180 days. Serum testosterone reached the normal range within 6 weeks after the end of suppression. During the interval of 112 days, 77.5% of the buserelin dose was released.

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 µg buserelin/g creatinine. The minimum therapeutic release rate was determined to be 3.5 µg/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 $t_{1/2}$ = 10 min., an intermediate $t_{1/2}$ = 26 min. and a prolonged $t_{1/2}$ = 90 minutes. The excess buserelin dose did not change the plasma elimination rate.

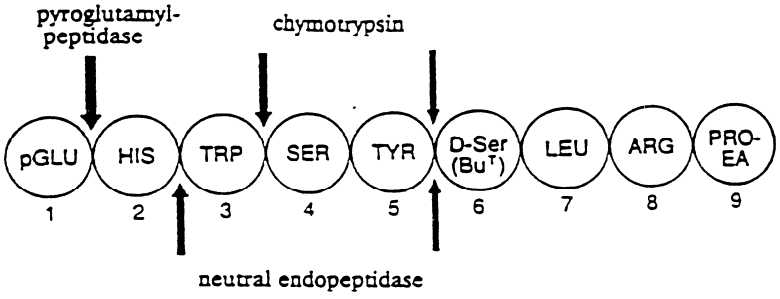
In further rat studies, buserelin 10 mcg/100 g bw/IV showed a physical $t_{1/2}$ in plasma of 3-6 minutes using RIA methods. In the 60 minutes post-dosing (1 mcCi ^{125}I-buserelin) about 20% more buserelin was cleared compared to the same dose of labelled LH-RH.

Organ Distribution

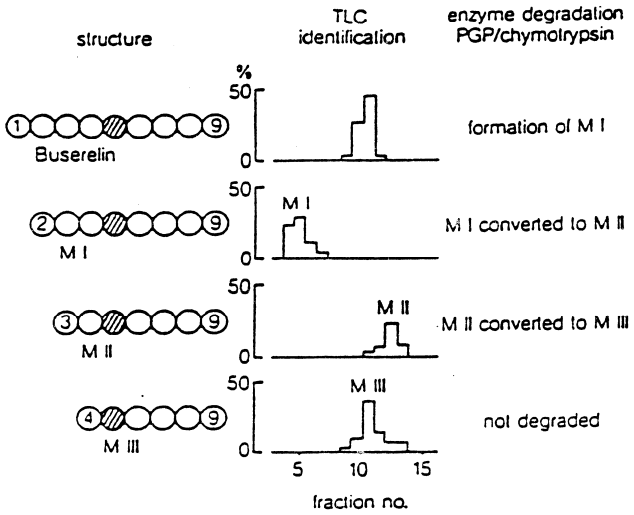
Two groups, each of 4 male rats, were given 1 mcCi of ^{125}I-buserelin (specific activity 200 mcCi/mg) or ^{125}I-LH-RH/IV and sacrificed 60 minutes post-dosing. Radioactivity was detected, in both groups, in liver, kidney, spleen, (skeletal) muscle and glands (adrenal, pituitary, thyroid, salivary). 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.



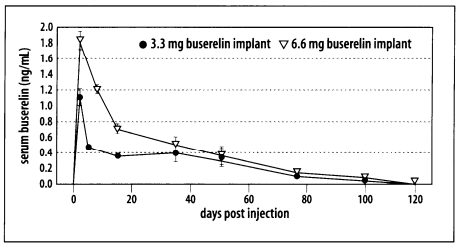
Identification of Buserelin metabolites in tissue extracts. (Left Panel) C-terminal Buserelin fragments of decreasing chain length, labeled in Tyr^5 with ^{125}I. (Middle panel) Chromatographic mobility on TLC plates (percent radio label per fraction). (Right panel) Products formed after sequential degradation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

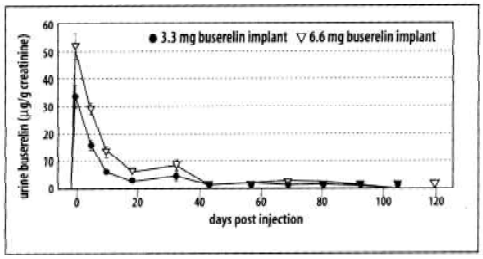
Buserelin metabolites in the urine of the mouse, rat, dog, monkey and human administered buserelin SC in isotonic saline or buserelin implants were investigated (by HPLC/RIA) in one study to assess whether the metabolism in animal species was similar to that in human. Similar types of metabolites were 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 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 1, 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.

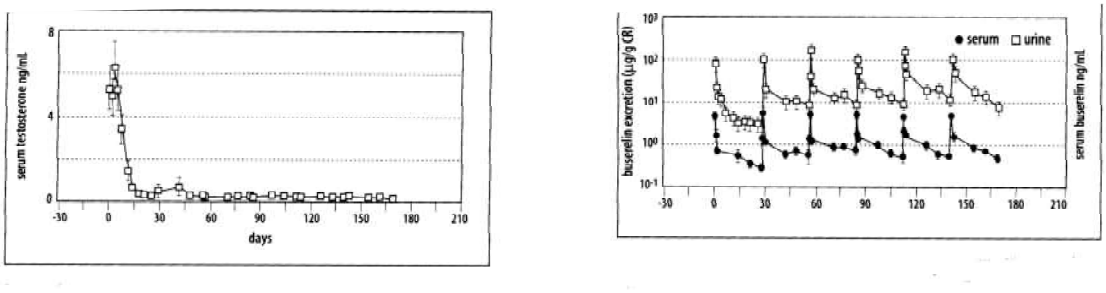




Pharmacokinetic profile of a single injection of a 3.3 mg or 6.6 mg buserelin acetate implant dose. Linear graphs of serum buserelin versus time and urinary buserelin versus time (RIA method).

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.

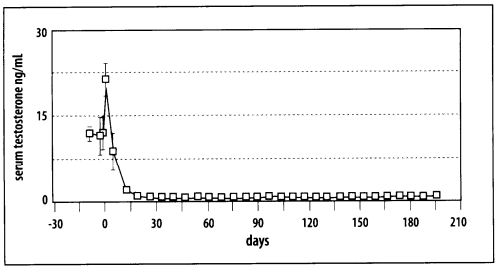


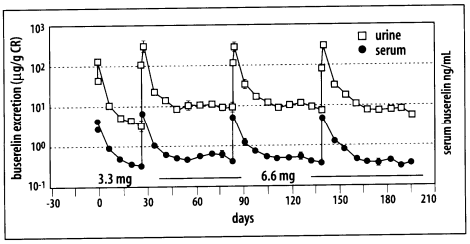
Graphical presentation of serum buserelin concentration, urinary buserelin excretion and serum testosterone concentration obtained after multiple administration of 3.3 mg buserelin implants, once every 4 weeks (RIA method).

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.

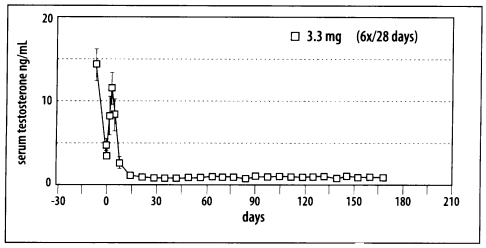


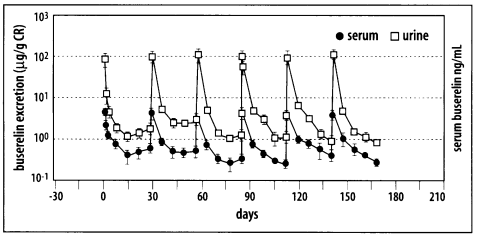


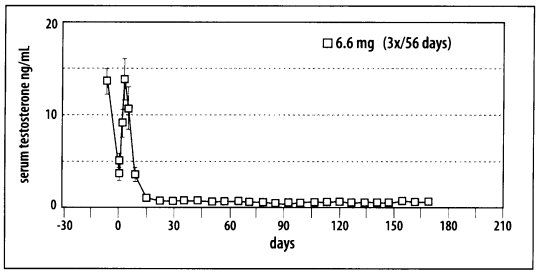
Graphical presentation of serum buserelin concentration, urinary buserelin excretion and serum testosterone concentration obtained after multiple administrations of 6.6 mg buserelin acetate implant following pretreatment with the 3.3 mg dose (RIA method).

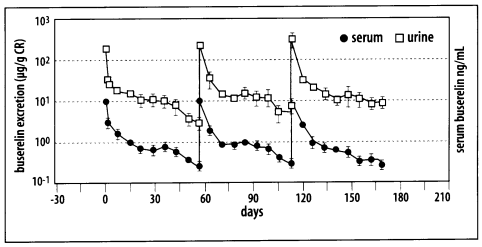
There was a correlation between the therapeutic buserelin levels measured in the urine and serum and the suppression of T secretion. At trough levels (urinary excretion of 3.0 and 6.0 Φg buserelin/g creatinine for the 3.3 mg and 6.6 mg dose, respectively), full T suppression was always maintained. No 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.







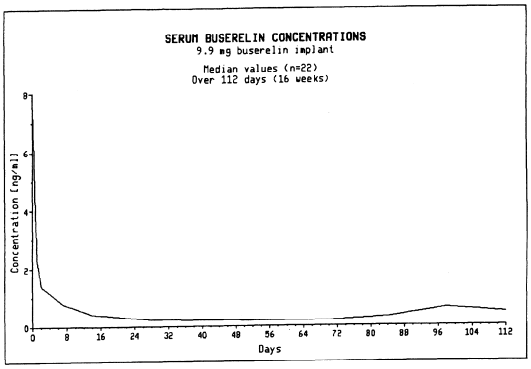


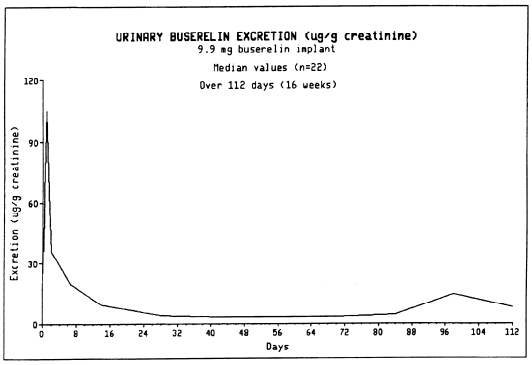
Graphical presentation of serum buserelin concentration, urinary buserelin excretion and serum testosterone concentration obtained after multiple administration of 3.3 mg or 6.6 mg buserelin acetate implants to patients pretreated with an antiandrogen (Groups 1 and 2, respectively) (RIA method).

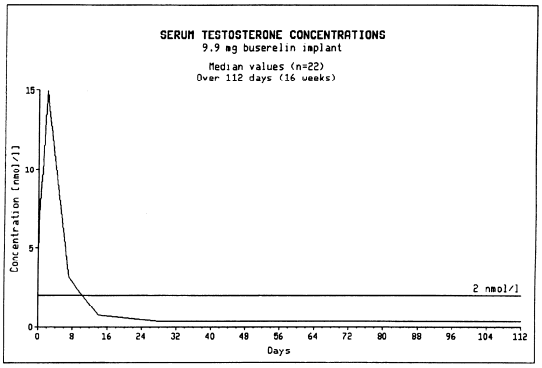
No stimulatory effect of the implant on LH and T secretion was found in Group 3 patients and none of these patients showed T values above castration levels at any time during the study. At C_{min} levels (urinary excretion of 6.0 and 4.4 µg buserelin/g creatinine for the 3.3 mg and 6.6 mg dose, respectively), 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.

SUPREFACT DEPOT 3 months (buserelin acetate implant)

To assess the pharmacokinetic profile of SUPREFACT DEPOT 3 months, a single dose study (n=22) was conducted in patients, (mean age 69.5 years), with prostatic cancer. The patients were administered single dose injections of SUPREFACT DEPOT 3 months (buserelin acetate equivalent to 9.45mg of buserelin base), and cyproterone acetate as comedication from 1 week before until 4 weeks after buserelin acetate injection. Buserelin showed a rapid release phase and a long-lasting release period of more than 3 months. The maximum serum concentration was reached about 4 hours after injection with a mean maximum concentration (C_{max}) of 8.11 ng/mL. Mean AUC (area under the serum concentration-time curve), calculated to the last sampling point, was 50 ngAday/mL. Mean serum buserelin concentration on day 112 was 0.52 ng/mL. Generally urinary excretion of buserelin remained above the target value of 1 µg/g creatinine during the entire study period (112 days)for all patients, thereby ensuring testosterone suppression. The mean percentage of time that buserelin remained above 1µg/g creatine in all patients was 96.8%. An initial rise in testosterone was seen in the first 48 hours. By day 7 testosterone had decreased in all patients. Mean time until castration range (castration range = 0-2 nmol/L serum testosterone concentration) was reached was 10 days. By week 4 and until the end of the study testosterone levels were well in the castration range.







Graphical presentation of serum buserelin concentration, urinary buserelin excretion and serum testosterone concentration obtained after single dose administration of SUPREFACT DEPOT 3 months (buserelin acetate implants equivalent to 9.45mg of buserelin base) to patients pretreated with an antiandrogen.

TOXICOLOGY

Local Tolerance

Local tolerance of subcutaneous injection of SUPREFACT DEPOT 2 months 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 µg/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 μg/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 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. 299 patients were included in the safety and efficacy analysis. All patients received SUPREFACT DEPOT 2 months 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. At admission patients were classified regarding their tumor status according to the American Urological System: 261 patients had stage D2 prostatic carcinoma, 32 had stage D1, 5 had stage C and the stage of disease was missing for 1 patient. The total duration of treatment was up to 75 months with a median of 20 months. The treatment duration can be summarized as follows:

Treatment Duration	*Number of Patients*
≤2months to 6 months	299
At least 1 year	271
At least 2 years	213
At least 3 years	133
At least 4 years	85
5 years or longer	60

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. 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 µg/300 µg t.i.d.; 20% treated SC with 200 µg 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 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	**Number of Patients Analyzed (n)**
summary over all criteria (NPCP, EORTC and ECOG)	
stable (or better) progression/progression suspected status missing not assessable	269 (70.0%) 16 (5.4%) 4 (1.3%) 10 (3.3%)
number of patients	*299 (100%)*

The table below summarizes the estimated survival rated for major time points and shows a regular decrease over the years.

Survival Analysis (Kaplan and Meier Rate Estimators)

Time Point	Estimated Survival Rate
Month 3	96%
Month 6	94%
Month 12	84%
Month 24	59%
Month 36	41%
Month 48	36%
Month 60	28%

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.

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. The median serum testosterone level decreased from 12.1 nmol/L on admission to 1.2 nmol/L at week 2, 0.7 nmol/L at month 2, then remaining stable for the rest of the 5 years. Thus the castration level (≤ 2 nmol/L) was reached within 2 weeks for 71% of the patients and for 90% of them within 2 months. At 4 month this rate increased to 93% and remained stable afterwards.

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: Two hundred and ninety-nine (299) patients were included in the safety analysis. Adverse drug reactions were reported by 79 patients. The most common drug reactions

are hot flushes, libido decrease, depression and hypertension (See ADVERSE REACTIONS). Most were caused by hormone deprivation.

Laboratory Investigations: Liver function test abnormalities were reported for four patients: one was attributed to alcohol abuse, one to liver metastases, one was stated as possibly related to cyproterone acetate treatment associated with heart failure and one subsequently presented stones in the choledochus. In the remaining biological criteria measured, no marked anomalies were detected as a trend in the study population.

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

SUPREFACT DEPOT 3 months (buserelin acetate implant)

An open label, non-comparative study, with 22 patients, was conducted to investigate the pharmacokinetics, pharmacodynamics and tolerability of buserelin implant 9.9 mg in patients with advanced prostatic carcinoma. All patients received a single dose of SUPREFACT DEPOT 3 months implant and all received concomitant antiandrogen treatment from 1 week before until 4 weeks after buserelin injection. All 22 patients who were enrolled, completed the study, which ended 16 weeks after a single buserelin injection.

Efficacy

Prostate size:

A decrease of 13% (95% confidence level of 7 to 19%) was observed by computer tomography when the anteroposterior prostate size at week 16 was compared with that at screening. For the transverse prostate size, from screening to week 16, a decrease of 18% (95% confidence interval of 14 to 23%) was observed.

Prostate-specific antigen:

The values of PSA tended to decrease from week 0 to week 16.

PSA Concentration (ng/mL)		% Change*	[95% CI]
Mean	Range		
Screening			
104.38	13.07-217.48		
Week 16			
15.18	DL-184.94	-89%	[-100; -55%]
Week 0 (Visit 3)			
84.92	9.41-215.25		
Week 16			
15.18	DL-184.94	-86%	[-100; -49%]

* % change and confidence interval (CIs) from ANOVA DL: detection limit = 5 ng/mL

Safety

Injection Site Reactions:

At injection, 15 patients reported mild pain (<15% on the visual analog scale). Five patients reported moderate pain (15 - 30%), and 2 patients reported severe pain (40% and 70%). Local tenderness was reported as mild.

Adverse Events:

All 22 patients reported at least 1 adverse event from buserelin injection onwards. Half of all patients reported symptoms coded for body as a whole (most often asthenia), 41% in the nervous system (most often hot flushes), and 41% in the urogenital system (most often impotence). The causal relationship of all these adverse events is difficult to assess because buserelin and cyproterone acetate, the comedication, work in a similar manner and therefore have a very similar adverse event pattern (See ADVERSE EVENTS).

BIBLIOGRAPHY

1. Adenauer H, Hellwich K. Endocrinological Treatment of Advanced Prostatic Cancer with Buserelin (HOE 766), an LH-RH Analogue. March 86. Data on file Hoechst Canada Inc.
2. Alibhai SMH, Gogov S, Allibhai Z. Long-term side effects of androgen deprivation therapy in men with non-metastatic prostate cancer: A systematic literature review. Critical Reviews in Oncology/Hematology 2006;60:201-15.
3. Behre HM, Sandow J, Nieschlag E. Pharmacokinetics of the Gonadotropin-Releasing Hormone Agonist Buserelin after Injection of a Slow-Release Preparation in Normal Men. Arzneimittelforsch Drug Res 1992;42(1):80-84.
4. Bélanger A, Labrie F, Lemay A, Caron S, Raynaud JP. Inhibitory effects of a single intranasal administration of D-SER(TBU)^{6}, des-Gly-$NH_2{}^{10}$ LH-RH ethylamide, a potent LH-RH agonist, on serum steroid levels in normal adult men. J Steroid Biochem 1980;13:123-126.
5. Bergquist C, Nillius SJ, Bergh T, Skarin G, Wide L. Inhibitory effects on gonadotrophin secretion and gonadal function in men during chronic treatment with a potent stimulatory luteinizing hormone-releasing hormone analogue. Acta Endocrinologica 1979;91:601-608.
6. Blom JHM, Hirdes WH, Schroder FH, De Jong FH, Kwekkeboom DJ, Van't Veen AJ, Sandow J, Krauss B. Pharmacokinetics and endocrine effects of the LH-RH analogue buserelin after subcutaneous implantation of a slow release preparation in prostatic cancer patients. Urol Res 1989;17:43-46.
7. Borgmann V, Hardt W, Schmidt-Gollwitzer M, Adenauer H, Nagel R. Sustained suppression of testosterone production by the luteinizing hormone-releasing hormone agonist buserelin in patients with advanced prostate carcinoma. The Lancet 1982; May 15:1097-1099.
8. Chen AC, Petrylak DP. Complications of androgen-deprivation therapy in men with prostate cancer. Current Urology Reports 2005;6:210-6.
9. Debruyne FMJ, Karthaus HFM, Schröder FH, de Voogt HJ, de Jong FH, Klijn JGM. Results of a Dutch phase II trial with the LH-RH agonist buserelin in patients with metastatic prostatic cancer. EORTC Genitourinary Group Monograph 2, Part A: Therapeutic Principles in Metastatic Prostatic Cancer 1985;251-270.
10. Faure N, Lemay A. Inhibition of testicular androgen biosynthesis by chronic administration of a potent LH-RH agonist in adult men. Archives of Andrology 1985;14:95-106.
11. Faure N, Lemay A, Laroche B, et al. Clinical response and safety of LH-RH agonist treatment in prostatic carcinoma. LH-RH and its analogues. Basic and clinical aspects. Proceedings of the International Symposium on LH-RH and its analogues 1984; June 28-30:312-325.

12. Faure N, et al. Preliminary results on the clinical efficiency and safety of androgen inhibition by an LH-RH agonist alone or combined with an anti-androgen in the treatment of prostatic carcinoma. The Prostate 1983;4:601.

13. Hatano T, Oishi Y, Furuta A, Iwamuro S, Tashiro K. Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer. BJY International 2000;86:449-452.

14. Heath M, Scanlon MF, Mora B, Snow MH, Gomez-Pan A, Watson MJ, Mulligan F, Hall R. The pituitary-gonadal response to the gonadotropin releasing hormone analogue D-Ser(TBU)^{6}-des-Gly^{10} LH-RH-ethyl-amide in normal men. Clin Endocrinol 1979;10:297-303.

15. Kwekkeboom DH, Lamberts SWJ, Blom JHM, Schroeder FH, De Jong FH. Prolonged treatment with the GnRH analogue buserelin does not affect alpha-subunit production by the pituitary gonadotroph. Clin Endocrinol 1990;32:443-451.

16. Lawrence JR, McEwen J, Pidgen AW, Robinson JD. Dose-response characteristics of D-Ser(TBU)^{6}-des-Gly^{10}-LH-RH-ethylamide (HOE 766 - Buserelin) following intranasal administration in five healthy male volunteers. Brit Pharmacol Soc 1981; September: 16-18.

17. Levine GN, D'Amico AV, Berger P, et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk : A science Advisory from the American Heart Association, American Cancer Society, and American Urological Association endorsed by the American Society for Radiation Oncology. Circulation 2010;121:833-40.

18. Martindale, Section Gonadorelin, Subsection Adverse Effects

19. Oefelein MG, Ricchuiti V, Conrad W, Seftel A, Bodner D, Goldman H, Resnick M. Skeletal Fracture Associated with Androgen Suppression Induced Osteoporosis: The Clinical Incidence and Risk Factors for Patients with Prostate Cancer. J Urol 2001;166(5):1724-1728.

20. An Open-Label Noncomparative Study of Buserelin in the Treatment of Patients with Stage C or Stage D Carcinoma of the Prostate and a Comparison with Historical Controls for Stage D2 (NPCP Protocols 500 and 1300). September 86. Data on file/ Hoechst Canada Inc.

21. Presant CA, Soloway MS, Klioze SS, et al. Buserelin as primary therapy in advanced prostatic carcinoma. Cancer 1985 56:2416-2419.

22. Periodic Safety Update Report for Buserelin for the Time Period 16-02-1996 to 15-07-1996.

23. Reznik Y, Chapon F, Lahlou N, Mahoudeau J. Pituitary apoplexy of a gonadotroph adenoma following gonadotrophin releasing hormone agonist therapy for prostatic cancer. J of Endocrinol. Invest. 1997;20:566-568.

24. Sandow J, Jerabek-Sandow G, Krauss B, Schmidt-Gollwitzer M. Pharmacokinetics and metabolism of LH-RH agonists, clinical aspects. LH-RH and its analogues. Basic and clinical aspects. Proceedings of the International Symposium on LH-RH and its analogues 1984; June 28-30:123-137.

25. Sandow J, Petri W. Intranasal administration of peptides. Biological activity and therapeutic efficacy. Transnasal Systemic Medications 1985;183-199.

26. Sandow J, von Rechenberg W, Jerzabek G, Engelbart K, Kuhl H, Fraser H. Hypothalamic-pituitary-testicular function in rats after supraphysiological doses of a highly active LH-RH analogue (buserelin). Acta Endocrinologica 1980;94:489-497.

27. Sandow J, von Rechenberg W, Jerzabek G, Stoll W. Pituitary gonadotropin inhibition by a highly active analog of luteinizing hormone-releasing hormone. Fertility and Sterility 1978;30(2):205-209.

28. Sandow J, von Rechenberg W, König W, Hahn M, Jerzabek G, Fraser H. Physiological studies with active analogues of LH-RH. Proceedings of the 2nd Eur. Coll. on hypothalamic hormones 1978; Weinheim, Germany.

29. Smith MR. Androgen deprivation therapy for prostate cancer: new concepts and concerns. Curr Opin Endocrinol Diabetes Obes 2007;14:247-54.

30. Stoch SA, Parker RA, Chen L, Bubley G, Ko YJ, Vincelette A, Greenspan SL. Bone Loss in Men with Prostate Cancer Treated with Gonadotropin-Releasing Hormone Agonists. J of Clin Endocrinol & Metabolism 2001; 86(6):2787-2791.

31. Waxman J, Williams G, Sandow J, Hewitt G, Abel P, Farah N, Fleming J, Cox J, O'Donoghue EPN, Sikora K. The clinical and endocrine assessment of three different antiandrogen regimens combined with a very long-acting gonadotropin-releasing hormone analog. Am J Clin Oncol 1988;II (suppl.2):S152-S155.

32. Waxman JH, Hendry WF, Whitfield HN, Oliver RTD. A long term follow-up of patients with advanced prostatic cancer treated with buserelin. EORTC Genitourinary Group Monograph 2, Part A: Therapeutic Principles in Metastatic Prostatic Cancer, 1985;271-277.

33. Wenderoth UK, Happ J, Krause U, Adenauer H, Jacobi GH. Endocrine studies with a gonadotropin-releasing hormone analogue to achieve withdrawal of testosterone in prostate carcinoma patients. Eur Urol 1982;8:343-347.

34. Wenderoth UK, Jacobi GH. Three years of experience with the GNRH-analogue buserelin in 100 patients with advanced prostatic cancer. LH-RH and its analogues. Basic and clinical aspects. Proceedings of the International Symposium on LH-RH and its analogues 1984; June 28-30:349-358.

35. Wibaux F, Cortet C, Assaker R, Soto-Ares G, Merlen E, Dewailly D. Effects of a GnRH Agonist injection on a gonoadotrope adenoma: A study of three cases. Congress of the French Endocrinology Soc. 2002;63(4):1-2