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Abbreviated Package Insert. See Product Monograph for complete product information.

P SUPREFACT® DEPOT 2 MONTHS
P SUPREFACT® DEPOT 3 MONTHS

Buserelin acetate implant / Buserelin base 6.3 mg
Buserelin acetate implant / Buserelin base 9.45 mg

Luteinizing Hormone-Releasing
Hormone (LH-RH) Analogue

F50051094H

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 INFORMA- TION]; patients who do not present with hormone-dependent carci- noma; 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 PRE- CAUTIONS]. At the start of treatment, there is a

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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 administra-tion 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 con- currently at the start of buserelin implant therapy may avoid the occur- rence 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 in-terval 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, Cardiovas-cular 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 aintake**)	
	n	%	n	%	n	%
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	4	1.3	--	--
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, thrombophlebitis

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, equiv-alent 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.

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.

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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.

Your physician and pharmacist are always your best source of information about your condition and treatment. If you have additional questions or concerns, be sure to ask them.

This document plus the full Product Monograph, prepared for health care professionals can be found at **www.xediton.com** or by contacting the importer/distributor, Xediton Pharmaceuticals Inc. at 1-888-XEDITON.

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