In hypertension or angina... Control That's Easy to Live With

HIGH RATE OF SUCCESS IN AN NIH-SPONSORED STUDY

83% of hypertensive patients — the highest percentage — remained on initial therapy with NORVASC® (amlodipine besylate) after 4 years; nearly all patients were on the 5-mg starting dose.

LOW RATE OF DISCONTINUATION

ONLY 1.5% of patients in placebo-controlled studies (n=1730) discontinued therapy due to adverse effects.

PROVEN SAFETY

No negative inotropic effects at clinical doses in hemodynamic studies.

No clinically significant effect on cardiac conduction or heart rate.

*Similar hemodynamic findings, however, have been observed with agents possessing significant negative inotropic effects.

Once-Daily NORVASC® (amlodipine besylate)

EFFICACY AND SAFETY THAT'S EASY TO LIVE WITH
In hypertension or angina, convenient once-daily dosing

- The usual starting dose is 5 mg in hypertension or angina.
  - In hypertension, small, fragile, or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg once daily.
- Titration can proceed to 10 mg.
  - Most angina patients will require 10 mg.
  - Can be taken with or without food.
- The most common side effects are headache and edema.

**Rx** NORVASC 5 mg #30 *Fig. 1* tablet per day

**Efficacy and Safety**

**NORVASC** (amlodipine besylate) Tablets

**Once-Daily 5-mg and 10-mg tablets**

**Brief Summary**

NORVASC (amlodipine besylate) Tablets

For Oral Use

**Contraindications:** NORVASC is contraindicated in patients with known sensitivity to amlodipine.

**Warnings/Special Cautions:** Treatment with NORVASC should be discontinued in patients with history of myocardial infarction, angina, or unstable angina, and those with exacerbation of congestive heart failure.

**Side Effects:** Headache and edema are the two most common symptoms observed in patients treated with NORVASC. Other side effects include dizziness, fatigue, dyspnea, chest pain, and palpitations.

**References**


**Pfizer Labs • NHO • Pratt • Roeing**

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The Journal of the American Society of Nephrology will publish original manuscripts judged by peers to be of high quality and relevant to the broad field of nephrology. Nephrology is an alliance of scientists and physicians who seek to understand the functions of the kidneys and the means to improve the medical care of individuals with kidney disease. The strength and vitality of the discipline radiate, historically, from the dynamic interaction between the basic and the clinical sciences. The Journal strives to nurture this relationship by providing the means for communicating to nephrologists and others in related specialties critical information of broad significance in the field. Subjects appropriate for the Journal include, but are not restricted to:

- clinical nephrology
- cell and transport physiology
- pathology and immunology
- cell and structural biology
- pathophysiology of renal disease
- hormones, autacoids and growth factors
- hemodynamics, hypertension and vascular regulation
- dialysis
- transplantation
- mineral metabolism and bone disease
- molecular medicine, genetics, and development

General Information

Original manuscripts are of two types: Regular Articles and Brief Communications. Regular Articles are traditional full length papers that address research questions with exhaustive experimental design and methodology. Brief Communications should contain not more than 2000 words (including abstract, figures, tables and references) describing important new observations in nephrology.

Reviews of basic and clinical topics of interest to the readership will be solicited by the editors.

In the cover letter, designate one author as the correspondent. The cover letter should include a statement explaining why the research is especially important. The journal office may solicit editorials to accompany articles that are especially newsworthy or controversial.

Include in the cover letter the names, addresses, telephone and fax numbers and areas of expertise of at least five individuals (peers) who may serve at the discretion of the editors, as reviewers of the manuscript.

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The signatures that must accompany the cover letter indicate that each author approved the final version of the manuscript and is prepared to take public responsibility for the work.

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- Submit an original manuscript and three photocopies, typed double-spaced in letter-quality print on one side only of standard (8½ × 11 inch) white bond paper. Manuscripts should be organized as follows: title page, abstract, introduction, methods, results, discussion, acknowledgments, references, tables and figure legends.
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- Abstract: State the problem considered, methods, results and conclusions in less than 250 words.
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3. Include a cover letter containing a copyright transfer statement.  
4. Include all authors’ personal signatures.  
5. Designate a corresponding author and provide a telephone number, fax number and address.

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Now, when enalapril or felodipine ER alone doesn’t control blood pressure sufficiently...

Consider the complementary action of LEXXEL

- Achieved significantly greater blood pressure control than either component alone, in clinical studies\(^1,2\)
- Provides the complementary action of the most frequently prescribed ACE inhibitor\(^3\) and a dihydropyridine calcium channel blocker
- Excellent tolerability profile in a wide range of patients\(^4\)
- Convenient once-a-day dosing in an easy-to-take tablet
- Costs 36% less, based on AWP, than combined individual prescriptions for two components\(^5\)

The AWP may not reflect the actual cost incurred by a patient in the purchase of each product.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, LEXXEL should be discontinued as soon as possible. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality.)

Angioedema may occur at any time during treatment. Discontinue LEXXEL at the first sign of angioedema and treat appropriately. It should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Angioedema.)

In clinical trials, the most common adverse events were headache, dizziness, and peripheral edema.

*Based on total prescriptions written from September 1995 through August 1996. Source: IMS.
\(^1\)Average Wholesale Price (AWP) at the recommended starting dosages for each product. Source: Medi-Span, Inc., October 1996.

Before prescribing LEXXEL, please see brief summary of Prescribing Information on the last page of this advertisement.
NEW
LEXXEL
5-5 mg
ENALAPRIL MALEATE • FELODIPINE ER
ONE TABLET • ONCE A DAY
COMPLEMENTARY ACTION FOR GREATER BLOOD PRESSURE CONTROL
LEXXEL® 5-5 mg
(EMLA® MALEATE-PHENOXYETHANOL) ON TABLETS

BRIEF SUMMARY
Read the full Prescribing Information.

INDICATIONS AND USAGE
LEXCEL is indicated for the treatment of hypertension. It is not indicated for the initial treatment of hypertension in patients with severe hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg).

Contraindications
LEXCEL is contraindicated in patients who are hypersensitive to any component of the product. Because of the enalapril content, LEXCEL is contraindicated in patients with a history of angioedema related to previous treatment with enalapril or other ACE inhibitors.

WARNINGS

Anaphylactic and Possibly Fatal Reactions: Presumably because angiotensin-converting enzyme (ACE) inhibitors affect the renin-angiotensin-aldosterone system, ACE inhibitors may cause anaphylactic and other allergic-type reactions, especially in patients who have been treated with angiotensin-converting enzyme inhibitors. These reactions are more common in patients with a history of angioedema and, therefore, may be expected in patients with idiopathic angioedema.

Anaphylactoid Reactions During Renal Therapy: Patients undergoing dialysis who receive ACE inhibitors are at increased risk of developing angioedema and exacerbation of their renal failure.

Severe Hypotension: ACE inhibitors may cause severe, sudden, and even fatal hypotension, especially in during the first dosing of enalapril (5 mg). Hypotension may occur within hours of starting therapy. ACE inhibitors cause the release of kinin and angiotensin II, which leads to increased plasma levels of renin. This may cause a reduction in the blood pressure. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Renal Maleate Excretion: Enalapril maleate is a salt of enalapril, which is eliminated primarily by the kidneys. Patients with renal impairment may be more susceptible to the effects of ACE inhibitors.

Increased Risk of Cardiac Arrest: Patients with reperfusion therapy and those who have not been treated with ACE inhibitors may have an increased risk of cardiac arrest.

Increased Risk of Hypotension: ACE inhibitors may cause hypotension in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Hyperkalemia: ACE inhibitors may cause hyperkalemia in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Hypoglycemia: ACE inhibitors may cause hypoglycemia in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Pulmonary Edema: ACE inhibitors may cause pulmonary edema in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Renal Failure: ACE inhibitors may cause renal failure in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Thrombocytopenia: ACE inhibitors may cause thrombocytopenia in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Agranulocytosis: ACE inhibitors may cause agranulocytosis in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Hypertension: ACE inhibitors may cause hypertension in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Hyponatremia: ACE inhibitors may cause hyponatremia in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Diabetes Mellitus: ACE inhibitors may cause diabetes mellitus in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Renal Insufficiency: ACE inhibitors may cause renal insufficiency in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Hypokalemia: ACE inhibitors may cause hypokalemia in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Hypernatremia: ACE inhibitors may cause hypernatremia in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Hypocalcemia: ACE inhibitors may cause hypocalcemia in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Hypomagnesemia: ACE inhibitors may cause hypomagnesemia in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

Increased Risk of Hypothyroidism: ACE inhibitors may cause hypothyroidism in patients with severe hypotension or with symptomatic bradycardia. Patients with severe hypotension or with symptomatic bradycardia should be treated with vasopressors.

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LEXCEL* (Enalapril Maleate-Felodipine ER) Tablets

Other clinical adverse events considered related (possibly, probably or definitely) to treatment with enalapril-felodipine ER that occurred with an incidence of less than one percent in the placebo-controlled, double-blind trial listed below. These events are listed in order of decreasing frequency within each category. Body as a Whole: Syncope, facial edema, orthostatic effects, chest pain; Cardiac: Palpitation, hypotension, bradycardia, premature ventricular contractions, increased heart rate; Digestive: Dry mouth, constipation, dyspepsia, flatulence, acid regurgitation, vomiting, diarrhea, nausea, anorexia, pain; Dermatological: Rash, pruritus, hair color change, alopecia, dry skin; Special Senses: Increased intraocular pressure; Drug-induced: Miosis, hot flashes.

Other infrequent adverse events were seen in clinical trials with enalapril-felodipine ER (causal relationship unknown). These include: Body as a Whole: Abdominal pain, fever; Digestive: Dental pain; Metabolic: Increased ALT and AST, hyperglycemia; Nervous System: Head pain, myalgia, headache, low back pain; Respiratory: Upper respiratory infection, rhinitis, pharyngitis, bronchitis; renal, conglutination, influenza, sinus disorder; Special Senses: Conjunctivitis; Drug-induced: Proteinuria, pyuria, urinary tract infection.

Enalapril Maleate: Other adverse event that have been reported with enalapril, without regard to causality, are listed (in decreasing severity) below. Angioedema: Angioedema has been reported in patients receiving enalapril maleate, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with LEXCEL should be discontinued and appropriate therapy instituted immediately (see WARNINGS). Body as a Whole: Anaphylactic reactions (see WARNINGS). Anaphylactic and Possibly Related Reactions; Cardiac: Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS). Hypotension, orthostatic hypotension, pulmonary edema and infarction, pulmonary edema, rhythm disturbances including atrial fibrillation, atrial arrhythmias, angina pectoris; Digestive: Diarrhea, nausea, vomiting, hepatitis (hematocrit decrease) (proven on rechallenge) or cholestatic jaundice (see WARNINGS), Hepatic Failure), melena, anorexia, glossitis, stomatitis; Gastrointestinal: Rare cases of neutropenia, thrombocytopenia and bone marrow depression; GI: Increased ALT, AST, GGT, alkaline phosphatase; Hematologic: Anemia, leukopenia, lymphopenia, thrombocytopenia; Hypersensitivity: Angioedema, drug rash, exfoliative dermatitis, pruritus, urticaria, pruritus, bronchospasm, angioneurotic edema; Immune System: Infections (see WARNINGS); Laboratory Test Findings: Serum Electrolytes: See PRECAUTIONS.

Creatinine: Minor reversible increases in serum creatinine were observed in patients treated with LEXCEL. Increases in creatinine are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and based on experience with other ACE inhibitors, would be expected to be especially likely in patients with severe renal dysfunction (see PRECAUTIONS).

Other: Minor reversible increases or decreases in serum potassium were infrequently observed in patients treated with LEXCEL; rarely were these measurements outside the normal range.


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December 1999
LEX03

References:
For effective intravenous treatment of iron deficiency anemia, it positively delivers.

Decreases total iron binding capacity.
Increases transferrin saturation.
For your patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible, depend on DEXFERRUM for quality intravenous treatment. Here's why:

- A recent study demonstrated that rapid iron utilization to replete iron stores and produce new hemoglobin takes place soon after DEXFERRUM administration.¹
- The study noted that DEXFERRUM significantly decreases total iron binding capacity and increases transferrin saturation.

<table>
<thead>
<tr>
<th></th>
<th>Pre-study</th>
<th>Week 1</th>
<th>Day 30</th>
<th>Effect of iron Dextran (probability value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum TIBC (μg/dL)</td>
<td>221.2 ± 40.9</td>
<td>201.3 ± 51.6</td>
<td>183.2 ± 48.6</td>
<td>0.0061</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>14.3 ± 2.8</td>
<td>32.3 ± 13.0</td>
<td>22.9 ± 3.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Study was conducted to determine the rate and extent of iron utilization after administration of intravenous iron dextran and to compare the efficacy of iron dextran of different molecular weights. Twenty patients were randomized to receive either a 500 mg dose of DEXFERRUM (267,000 daltons) or INFUSPOR (96,000 daltons) administered in five sequential 100 mg doses. Indices of iron status were examined before treatment and at weekly intervals up to four weeks later.

- The safety and efficacy of DEXFERRUM have been confirmed through clinical trials in end-stage renal disease (ESRD) patients on epoetin alfa.²

For more information, or to order DEXFERRUM, call us toll-free at 1-800-645-1706.

Call our Reimbursement Hotline at 1-800-282-7712 regarding DEXFERRUM reimbursement issues or our Patient Assistance Program. In the Washington, D.C., metropolitan area call 1-202-942-2453.

Warning

The parenteral use of complexes of iron and carbohydrates has resulted in anaphylactic-type reactions. Deaths associated with such administration have been reported. Therefore, DEXFERRUM should be used only in those patients in whom the indications have been clearly established and laboratory investigations confirm an iron-deficient state not amenable to oral iron therapy.

DEXFERRUM
(IRON DEXTRAN INJECTION, USP)

2. Data on file at American Regent Laboratories, Inc.

Please see brief summary of the prescribing information on the following page.
WARNING
THE PARENTERAL USE OF COMPLEXES OF IRON AND CARBOHYDRATES HAS RESULTED IN ANAPHYLACTIC-LIKE REACTIONS. DEATHS ASSOCIATED WITH SUCH ADMINISTRATION HAVE BEEN REPORTED. THEREFORE, DEXFERRUM SHOULD BE USED ONLY IN THOSE PATIENTS IN WHOM THE BENEFIT IS CONSIDERED TO OUTWEIGH THE POTENTIAL RISKS. CLINICAL TRIALS INVESTIGATING COMBINATION IRON DEPENDENT STATE NOT AMENABLE TO ORAL IRON THERAPY.

DESCRIPTION: DEXFERRUM [iron dextran injection, USP] is a dark brown, slightly viscous sterile liquid complex of ferric pyrophosphate and a low molecular weight dextran derivative for intravenous use. Each mL contains 50 mg elemental iron as an iron dextran complex. Sodium citrate may be added to titrate. Water for injection (pH adjusted to 5.2 - 5.5 with hydrochloric acid and, if necessary, sodium hydroxide. Sterile, nonpyrogenic.

Therapeutic Class: Hematologic.

INDICATIONS AND USAGE: Dextran is indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.

CONTRAINDICATIONS: Hypersensitivity to the product. All anemias not associated with iron deficiency.

WARNINGS: See BOXED WARNING.

A risk of anaphylaxis may attend the intravenous injection of iron-carbohydrate complexes. Such complexes have been found under experimental conditions to produce anemia when large doses or small doses injected repeatedly at the same site were given to rats, mice, and rabbits, and possibly in humans.

The long latent period between the injection of a potential cardiohazard and the appearance of the tumor makes it impossible to measure accurately the risk in man. There have, however, been several reports in the literature describing tumors at the injection site in humans who had previously received intravenous injections of iron-carbohydrate complexes.

Large intravenous doses, such as used with total dose infusions (TDI), have been associated with an increased incidence of adverse effects. The adverse effects frequency are divided (1:50) reactions reported by one or more of the following symptoms: anaphylaxis, backache, chills, dizziness, nausea to high fever, headache, malaise, myalgia, nausea, or vomiting. The onset is usually 24-48 hours after administration and symptoms generally subside within 3-4 days. The strategy of these reactions is not known. The potential for a delayed reaction must be considered when estimating the risk/benefit of treatment.

The maximum daily dose should not exceed 3 mL, undiluted iron dextran.

This preparation should be used with extreme care in patients with serious impairment of liver function.

It should not be used during the acute phase of infectious kidney disease.

Adverse reactions experienced following administration of Dexferrum may exacerbate cardiovascular complications in patients with pre-existing cardiovascular disease.

PRECAUTIONS: General: Uncommon therapy with parenteral iron will cause excess storage of iron with the consequent possibility of excessive hemosiderosis. Such iron overload is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias that might be erroneously diagnosed as iron deficiency anemias.

Dexferrum should only be used in individuals with histories of significant allergies and/or anemias. Anaphylactic and other hypersensitivity reactions have been reported after unsuccessful test doses as well as therapeutic doses of iron dextran injection. Therefore, administration of subsequent test doses should be considered. (See DOSAGE AND ADMINISTRATION: Administration.)

Subcutaneous or intramuscular injections: (5 mL of 1:2000 solution, by subcutaneous or intramuscular injection.) Notice: Patients using beta-blocking agents may not respond adequately to asperepsy. Improvement or similar beta-blocking agents may be required in these patients.

Patients with rheumatoid arthritis may have an acute exacerbation of joint pain and swelling following the administration of Dexferrum.

Information For Patients: Patients should be advised of the potential adverse reactions associated with the use of Dexferrum.

Dosage and Administration: Large doses of iron dextran (5 mL, or more) have been reported to give a brown color to serum from a blood sample drawn 4 hours after administration. The drug may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

Serum iron determinations (especially by colorimetric assay) may not be meaningful for 3 weeks following the administration of iron dextran.

Serum ferritin peaks approximately 7 to 8 days after an intravenous dose of Dexferrum and slowly returns to baseline after about 3 weeks.

Examination of the bone marrow for iron stores may not be meaningful for prolonged periods following iron dextran therapy because residual iron dextran may remain in the reticuloendothelial cells.

Some scarce with T1-weighted bone seeking agents. In the presence of high serum ferritin levels or following iron dextran infusions, these agents have been reported to show reduction of bony uptake, marked renal activity, and excessive blood pool and soft tissue accumulation.

Carcinogenesis, Mutagenesis, Impairment Of Fertility: See WARNINGS.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Iron dextran has been shown to be teratogenic and embryotoxic in mice, rats, rabbits, dogs, and monkeys when given in doses of about 3 times the maximum human dose.

No consistent adverse fetal effects were observed in mice, rats, rabbits, dogs and monkeys at doses of 50 mg/kg or less. Fetal and maternal toxicity has been reported in monkeys at a total intravenous dose of 50 mg/kg over a 14 day period. Similar effects were observed in mice and rats on administration of a single dose of 120 mg/kg. Prenatal abnormalities in rats and dogs were observed at doses of 250 mg/kg and higher. The animals used in these tests were not iron deficient. There are no adequate and well-controlled studies in pregnant women. Dexferrum should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnant Travellers: Various animal studies and studies in pregnant human have demonstrated insufficient results with respect to the potential transfer of iron dextran as iron dextran. It appears that some iron does reach the fetus, but the form in which it crosses the placenta is not clear.

Nursing Mothers: Caution should be exercised when Dexferrum is administered to a nursing woman. Traces of unmetabolized iron dextran are excreted in human milk.

Pediatric Dosage: Use: not recommended for use in infants under 4 months of age (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: Systemic: Fatal anaphylactic reactions have been reported with the use of iron dextran injections. On occasion these reactions have been fatal. Such reactions, which occur most often within the first several minutes after injection, usually manifest themselves as a wide variety of cardiovascular collapse. (See boxed WARNING AND PRECAUTIONS: General, pertaining to immediate availability of epinephrine.)

Cardiovascular: Chest pain, chest tightness, shock, hypotension, hypertension, tachycardia, flushing, arrhythmias. (Flushing and hypotension may occur from too rapid injections by the intravenous route.)

Dermatologic: Urticaria, pruritus, purpura, rash.

Gastrointestinal: Abdominal pain, nausea, vomiting, diarrhea.

Hematologic/Hematopoietic: Leukocytosis, lymphocytosis.

Miscellaneous: Localized iron deposits in tissues with quiescent rheumatoid arthritis (See PRECAUTIONS: General). myalgia, backache, sterile abscesses, brown iron and/or underlying tissue discoloration (staining), cellulitis, swelling, inflammation, local phlebitis at or near intravenous injection site.

Neurologic: Convulsions, seizures, syncope, headache, weakness, unresponsiveness, paraparesis, facial palsy, epistaxis, chills, dizziness, disorientation, numbness.

Respiratory: Respiratory arrest, dyspnea, bronchospasm.

Urologic: Hematuria.

Delayed Reactions: Anaphylaxis, backache, chills, dizziness, fever, headache, malaise, myalgia, nausea, vomiting (See WARNINGS).}

Miscellaneous: Faintness; epistaxis, sweating, shivering, chills, malaise, altered taste.

DOSAGE AND ADMINISTRATION: Oral iron should be discontinued prior to administration of Dexferrum.

Dosage: Background: PRIOR TO RECEIVING THEIR FIRST DEXFERRUM THERAPEUTIC DOSE, ALL PATIENTS SHOULD BE GIVEN AN INTRAVENOUS TEST DOSE OF 0.5 mL (See PRECAUTIONS: General). THE TEST DOSE SHOULD BE ADMINISTERED AT A GROUND RATE OF 0.1 mL PER MINUTE. ALTHOUGH ANAPHYLACTIC REACTIONS ARE KNOWN TO OCCUR FOLLOWING DEXFERRUM ADMINISTRATION THEY ARE USUALLY SPONTANEOUS WITHIN A FEW MINUTES, OR SOONS. IT IS RECOMMENDED THAT A PERIOD OF AN HOUR OR MORE BE SUSTAINED IN THE ABSENCE OF FURTHER ANAPHYLACTIC REACTIONS. INDIVIDUAL DOSES OF 2 mL, OR LESS MAY BE GIVEN ON A DAILY BASIS UNLESS THE TOTAL CALCULATED AMOUNT REQUIRED HAS BEEN RECEIVED. DEXFERRUM IS GIVEN UNFLAVORED AT A STEADY GRADUAL RATE NOT TO EXCEED 50 MG (1 mL) PER MINUTE.

If no adverse reactions are observed, Dexferrum can be given according to the following schedule until the calculated total amount required has been reached. Each daily dose should ordinarily not exceed 0.5 mL (25 mg) of iron for infants under 5 kg (11 lbs); 1 mL (50 mg) of iron for children under 10 kg (22 lbs); and 2 mL (100 mg) of iron for other patients.

DOSAGE: The dose of Dexferrum with other medications or added to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

HOW SUPPLIED: Dexferrum [iron dextran injection, USP] containing 50 mg of elemental iron per mL, is available in 2 mL single dose vials (for intravenous use) in containers of 10 (NDC 0177-0034-10) and individually packaged (NDC 0177-0034-01). Store at controlled room temperature 15 - 30°C (59 - 86°F). CAUTION: Federal law prohibits dispensing without prescription. This is a brief summary; see product package insert for full prescribing information.

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- Broadens your dosing range, allowing you to provide treatment commensurate with PTH levels.
- Corresponds to the practice of nephrology thought leaders for patients with markedly elevated PTH.

**Dosing highlights**

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<th>Enhanced therapy</th>
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<td>0.5-1 mcg q 2-4 weeks</td>
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Enhanced Calcijex® (Calcitriol Injection) therapy refers to changes in dosing guidelines to encourage therapy commensurate with PTH level. Calcijex has *not* changed, only the suggested dosing guidelines as reflected in the accompanying brief disclosure.

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Representative patient with severe hyperparathyroidism: Initial 2 mcg calcitriol dose, 3 x per week increased incrementally to 6 mcg, 3 x per week. PTH decreased dramatically.¹ Measures to control calcium intake, including a low-calcium dialysate and strict control of phosphorus levels, limited hypercalcemia.
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1 mcg and 2 mcg/mL.

BRIEF SUMMARY

INDICATIONS AND USAGE
Calcitriol (calcitriol injection) is indicated in the management of hypocalcemia in patients undergoing chronic renal dialysis. It has been shown to significantly reduce elevated parathyroid hormone levels. Reduction of PTH has been shown to result in an improvement in renal osteodystrophy.

CONTRAINDICATIONS
Calcitriol (calcitriol injection) should not be given to patients with hypercalcemia or evidence of vitamin D toxicity.

WARNINGS

1. Precautions

- Excessive dosage of Calcitriol (calcitriol injection) induces hypercalcemia and in some instances hypercalcemic osteodystrophy, therefore, early in treatment during dosage adjustment, serum calcium and phosphorus should be determined at least twice weekly. Should hypercalcemia develop, the drug should be discontinued immediately.

- Calcitriol should be given cautiously to patients on dialysis, because hypercalcemia in such patients may progress rapidly.

2. Information for the Patient

- The patient and his or her parents should be informed about adherence to instructions about diet and calcium supplementation and avoidance of the use of unapproved non-prescription drugs, including magnesium-containing antacids. Patients should also be carefully informed about the symptoms of hypercalcemia (see ADVERSE REACTIONS).

3. Essential Laboratory Tests

- Serum calcium, phosphorus, magnesium and alkaline phosphatase and 24-hour urinary calcium and phosphorus should be determined periodically. During the initial phase of the medication, serum calcium and phosphorus should be determined on a monthly basis (weekly or twice weekly).

- Abnormal bone disease may develop if PTH levels are suppressed to abnormal levels. If biopsy is not being done, the paired bone scan may be used to determine the rate of bone turnover. PTH serum levels should fall below recommended target range (1.5 to 3 times the upper limit of normal) in patients treated with Calcitriol, the Calcitriol dose should be reduced or therapy discontinued. Discontinuation of Calcitriol therapy may result in rebound hyperparathyroidism; therefore, careful titration of maintenance dose is recommended.

- Drug Interactions

- Magnesium-containing antacids and Calcitriol should not be concomitantly used, because such use may lead to the development of hyperparathyroidism.

- Cardiovascular, Myocardial, Impairment of Fertility

- Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Calcitriol (calcitriol injection). There was no evidence of mutagenicity as studied by the Ames Method. No significant effect on fertility was observed in animal studies reported using oral calcitriol.

- Use in Pregnancy: Pregnancy Category C

- Calcitriol given orally has been reported to be teratogenic in rabbits when given in doses 4 and 15 times the dose recommended for human use.

- Administration of 2.3 times of these doses showed external and skeletal abnormalities. However, none of the other 23 (150) fetuses showed significant abnormalities compared with controls.

- Teratology studies in rats showed no evidence of teratogenic potency. There are no adequate and well-controlled studies in pregnant women. Calcitriol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- Nursing Mothers

- It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from calcitriol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

- Pediatric Use

- Safety and efficacy of Calcitriol in pediatric patients have not been established.

- ADVERSE REACTIONS

- Adverse effects of Calcitriol (calcitriol injection) are, in general, similar to those encountered with excessive vitamin D intake. The early and late signs and symptoms of vitamin D intoxication are associated with hypercalcemia include:

- 1. Early

- - Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain and metallic taste.

- 2. Late

- - Polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinitis, and sneezing, increased BUN, albuminuria, hypercalcemia, elevated S027 and S026, eclamptic calcification, hypertension, cardiac arrhythmias and, rarely, overt psychosis.

- Occasional mild pain on injection has been observed.

OVERDOSAGE

Administration of Calcitriol (calcitriol injection) to patients in excess of their requirements can cause hypercalcemia, hypercalciumia and hyperphosphatemia. High intake of calcium and phosphorus concomitant with Calcitriol may lead to additional severe effects.

1. Treatment of Hypercalcemia and Overdose in Patients on Hemodialysis

- General treatments of hypercalcemia (greater than 1 mg/d) should be accompanied by the use of oral chelating agents and/or increased dialysis time and/or increased dialysate calcium. Serum calcium levels should be determined daily until normalization ensues. Hypercalcemia usually resolves in two to seven days. When serum calcium levels have returned to within normal limits, Calcitriol therapy may be reinstated at a dose 0.5 mcg less than prior therapy. Serum calcium levels should be obtained at least twice weekly after all dosage changes.

- Persistent or markedly elevated serum calcium levels may be corrected by dialysis against a calcium-free dialysate.

2. Treatment of Accidental Overdose of Calcitriol Injection

- The treatment of acute accidental overdose of Calcitriol should consist of general supportive measures. Serial serum electrolyte determinations (especially calcium), rate of urinary calcium excretion and assessment of electrolyte balance are also important. Confirmation that the patient is receiving digitalis. Discontinuation of supplemental calcium and low calcium diet are also indicated in accidental overdose. Due to the relatively short duration of the pharmacological action of calcitriol, further measures are probably unnecessary. Should, however, persistant and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives which may be considered, depending on the patient's underlying condition. These include the use of drugs such as phosphates and corticosteroid as well as measures to induce an appropriate forced diuresis. The use of peritoneal dialysis against a calcium-free dialysate has also been reported.

NOW SUPPLIED
Calcitriol (calcitriol injection) is supplied in 1 mL ampule containing 1 mcg (List No. 1280) and 2 mcg (List No. 1281).

Product from light.
Store at controlled room temperature 15° to 30°C (59° to 86° F).

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*Based on a nationwide survey of nephrologists. Data on file, Savage Laboratories.
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DESCRIPTION
CONTENTS: Each brown soft gelatin capsule contains: ferrous fumarate USP, 460 mg (151 mg elemental iron), ascorbic acid USP, 60 mg, folic acid USP, 1 mg, cyanocobalamin USP, 10 mcg.

DISCUSSION: The amount of elemental iron and the absorption of the iron components of commercial iron preparations vary widely. It is further established that certain “accessory components” may be included to enhance absorption and utilization of iron. Chromagen® Forte Capsules are formulated to provide the essential factors for a complete, versatile hematocrit.

ACTIONS
HIGH ELEMENTAL IRON CONTENT: Ferrous fumarate, used in Chromagen® Forte Capsules, is an organic iron complex which has the highest elemental iron content of any hematetic salt - 33%. This compares with 20% for ferrous sulfate (heptahydrate) and 13% for ferrous gluconate. Chromagen® Forte contains 151 mg of elemental iron.

MORE COMPLETE ABSORPTION: It has been repeatedly shown that ascorbic acid, when given in sufficient amounts, can increase the absorption of ferrous iron from the gastrointestinal tract.1,4,6,8,9 The administration-promoting effect is mainly due to the reduced action of ascorbic acid within the gastrointestinal lumen, which helps to prevent or delay the formation of insoluble or less dissociated ferric compounds. 3

PROMOTES MOVEMENT OF PLASMA IRON: Ascorbic acid also plays an important role in the movement of plasma iron to storage deposits in the tissues. 10 The action, which leads to the transport of plasma iron to ferritin, presumably involves its reducing effect, converting transferrin iron from the ferric to the ferrous state. 11 There is also evidence that ascorbic acid improves iron utilization, presumably as a further result of its reducing action, 10,11 and some evidence that it may have a direct effect upon erythropoiesis. Ascorbic acid is further alleged to enhance the conversion of folic acid to a more physiologically active form, folic acid, which would make it even more important in the treatment of anemia since it would aid in the utilization of dietary folic acid. 11

EXCELLENT ORAL TOLERATION: Ferrous fumarate is used in Chromagen® Forte Capsules because it is less likely to cause the gastric disturbances so often associated with oral iron therapy. Ferrous fumarate has a low ionization constant and high solubility in the entire pH range of the gastrointestinal tract. It does not precipitate proteins or have the astringency of more ionizable forms of iron, and does not interfere with proteolytic or diastatic activities of the digestive system. Because of excellent oral toleration, Chromagen® Forte Capsules can usually be administered between meals when iron absorption is maximal.

FOLIC ACID SUPPLEMENTATION: The use of supplemental folic acid may be indicated in patients with increased requirements for this vitamin, such as iron deficiency anemia. Folic acid administration may reduce the risk of neural tube defects in the developing fetus. 12 Folic acid has also been shown to reduce circulating homocysteine levels in the blood. 13,14 Folate as 5-methyltetrahydrofolate and B12 as methylcobalamin are involved in the remethylation reaction of homocysteine to methionine. 15,16 Elevated homocysteine plasma levels are associated with increased risk of preeclampsia, neural tube defects, myocardial infarction and arteriosclerosis. 17,18

TOXICITY: Ferrous fumarate was found to be the least toxic of three popular oral iron salts, with an oral LD50 of 630 mg/kg. In the same report, the LD50 of ferrous gluconate was reported to be 320 mg/kg and ferrous sulfate 230 mg/kg. 1,13

INDICATIONS
For the treatment of all anemias responsive to oral iron therapy, such as hypochromic anemia associated with pregnancy, chronic or acute blood loss, dietary restriction, metabolic disease and post-surgical convalescence.

CONTRAINDICATIONS
Hemochromatosis and hemosiderosis are contraindications to iron therapy. Folic acid is contraindicated in patients with pernicious anemia (see PRECAUTIONS).

SIDE EFFECTS
Average capsule doses in sensitive individuals or excessive dosage may cause nausea, skin rash, vomiting, diarrhea, precordial pain, or flushing of the face and extremities.

PRECAUTIONS
Folic acid should not be prescribed until the diagnosis of pernicious anemia has been eliminated, since it can alleviate the hematologic manifestations, while allowing neurological damage to continue undetected. 14

DOSAGE AND ADMINISTRATION
Usual adult dose is 1 soft gelatin capsule daily.

HOW SUPPLIED
Capsules: NDC 0281-0262-53, Bottle of 100
NDC 0281-0262-56, Bottle of 500

CAUTION: Federal law prohibits dispensing without prescription.

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Training in Nephrology *(Give *inclusive* dates for residences, fellowships, other relevant postgraduate education.)*

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List your five *most significant* publications.

Describe your clinical experiences as a specialist and consultant in kidney disease and related conditions that would provide basis for qualification of membership.

List other societies to which you belong.

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Nutropin AQ™
[somatropin (rDNA origin) injection]
The Only Growth Hormone That Doesn’t Require Reconstitution
“There’s no reconstitution so it’s easier to use. We like that. And so do our patients.”

Fewer steps to greater convenience
Nutropin AQ eliminates all of the steps necessary for a patient or parent to reconstitute lyophilized growth hormone.

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Nutropin AQ significantly reduces training time compared to lyophilized growth hormone products.

Ideal for families who are new to growth hormone therapy
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“It’s easier to train families to use AQ. And that saves me time!”

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Nutropin AQ™
[somatropin (rDNA origin) injection]

For more information, contact your Genentech representative or call Genentech Customer Service at 1-800-551-2231.

Please see accompanying full prescribing information for Nutropin AQ.
Nutropin AQ® (somatropin (DNA origin) injection) is also indicated for the long-term treatment of short stature associated with Turner syndrome.

CONTRAINdications
Nutropin AQ should not be used in subjects with closed epiphyses.

Nutropin AQ (somatropin (DNA origin) injection) should not be used in patients with active neoplasia. Growth hormone therapy should be discontinued if evidence of neoplasia develops.

WARNINGS
None.

PREcautionS
General. Nutropin AQ should be prescribed by physicians experienced in the diagnosis and management of patients with growth failure due to GHD deficiency, Turner syndrome or chronic renal insufficiency. No studies have been completed of Nutropin AQ therapy in patients who have received renal transplants. Currently, treatment of patients with functioning renal allografts is not indicated.

Because Nutropin AQ may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance.

Patients with a history of an intracranial lesion should be examined frequently for progression or recurrence of the lesion.

Patients with growth failure secondary to chronic renal insufficiency should be examined periodically for evidence of progression of the renal disease. Increased urinary protein excretion may be an early sign of renal deterioration.

Patients with known or untreated Turner syndrome patients. Physicians should be alert to these abnormalities, which may manifest during growth hormone therapy.

Patients with Turner syndrome should be evaluated carefully for debilitating orthopedic and other end organ abnormalities since these patients have an increased risk of heart or hearing disorders. In a randomized-controlled trial, there was a statistically significant increase in the incidence of aortic dissection and stroke in Turner syndrome patients compared to normal control patients. In all reported cases, RH-associated signs and symptoms resolved after termination of therapy or a reduction of the growth hormone dose. Funduscopic examination of patients is recommended at the initiation and periodically during the course of growth hormone therapy. Patients with Turner syndrome may be at increased risk for development of all.

As for any protein, local or systemic allergic reactions may occur. Patients/Parent should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Laboratory Tests: Serum levels of inorganic phosphorus, alkaline phosphatase, and parathyroid hormone (PTH) may increase with Nutropin AQ therapy.

Uncontrolled hypertension prevents optimal response to Nutropin AQ. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease. Changes in thyroid hormone laboratory measurements should be monitored during Nutropin AQ therapy. Therefore, patients should be informed about thyroid hormone abnormalities, which may manifest during growth hormone therapy.

Drug Interactions. The use of Nutropin AQ® (somatropin (DNA origin) injection) in patients with CRI receiving glucocorticoid therapy has not been evaluated. Concomitant glucocorticoid therapy may influence the growth-promoting effect of Nutropin AQ. If glucocorticoid replacement is required, the glucocorticoid dose should be carefully adjusted.

There was no evidence in the controlled studies of somatropin's interaction with drugs commonly used in CRI patients. Limited published data indicate that growth hormone treatment increases cytochrome P450 (CP450) mediated antithrombin clearance. Therefore, Nutropin AQ administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., colestipol, sex steroids, anti-inflammatories, cyclosporines). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes.

Carcinogenesis. Mutagenesis. Impairment of Fertility: Carcinogenicity, mutagenicity and reproductive studies have not been conducted with Nutropin AQ.

Pregnancy: Pregnancy (Category C). Animal reproduction studies have not been conducted with Nutropin AQ. It is not known whether Nutropin AQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nutropin AQ should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether Nutropin AQ is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nutropin AQ is administered to a nursing mother.

Information for Patients: Patients being treated with growth hormone and/or their parents should be informed of the potential benefits and risks associated with treatment. If home use is determined to be desirable by the physician, instructions on appropriate use should be given, including a review of the contents of the Patient Information Insert. This information is intended to aid in the safe and effective administration of the medication. It is not a disclosure of all possible adverse or intended effects.

If home use is prescribed, a prescription resistant container for the disposal of used syringes and needles should be recommended to the patient. Parents and/or parents should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes (see Patient Information Insert).

ADVERSE REACTIONS
As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. Growth hormone antibody binding capacities below 2 mg/L have not been associated with growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth attenuation has been observed, in clinical studies of patients that were treated with Nutropin® (somatropin (DNA origin) for injection) for the first time, G1/07 growth hormone deficient (GHD) patients, G125 CRI patients and G012 Turner syndrome patients screened for antibody production and/or developed antibodies with binding capacities ≥2 mg/L in six months, in a clinical study of patients that were treated with Nutropin AQ® (somatropin (DNA origin) for injection) for the first time, G031 CRI patients screened for antibody production for up to 12 months, developed antibodies with binding capacities ≥2 mg/L.

Additional short-term immunologic and renal function studies were carried out in a group of patients with CRI after approximately one year of treatment to detect other potential adverse effects of antibodies to growth hormone. Testing included measurements of C1q, C3, C4, rheumatoid factor, creatinine, creatinine clearance, and BUN. No adverse effects of growth hormone antibodies were noted.

In addition to an evaluation of compliance with the prescribed treatment program and thrombosis testing, testing for antibodies to human growth hormone should be performed periodically during treatment.

Injection site discomfort has been reported. This is more commonly observed in children switched from another growth hormone product to Nutropin AQ.

Nutropin AQ therapy is intended for treatment of patients as a single daily injection. In some cases, the injection site has changed with continued Nutropin AQ therapy.

Lactation: Lactating women should not breastfeed during treatment. The effects of Nutropin AQ on the human milk are not known. It is not known whether Nutropin AQ is excreted in human milk. It is not known whether Nutropin AQ therapy is transferred to the nursing infant. It is recommended that nursing be discontinued while the mother is receiving treatment with Nutropin AQ.

Other adverse drug reactions that have been reported in growth hormone-treated patients include the following: 1) Metabolic: Infrequent, mild and transient peripheral edema. 2) Musculoskeletal: Arthralgias, rare carpal tunnel syndrome. 3) Skin: Rare increased growth of pre-existing new, patients should be monitored carefully for malignant transformation. 4) Endocrine: Rare gynecomastia. Rare pancreatitis.

OVERDOSAGE
The recommended dosage for growth hormone deficiency is up to 0.30 mg/kg (approximately 0.90 kU/kg) of body weight weekly. The recommended dosage for chronic renal insufficiency is up to 0.30 mg/kg (approximately 1.05 kU/kg) of body weight weekly. The recommended dosage for Turner syndrome is up to 0.375 mg/kg (approximately 1.125 kU/kg) of body weight weekly. Long-term overdose could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

DOSEAGE AND ADMINISTRATION
The Nutropin AQ® (somatropin (DNA origin) injection) dosage and administration schedule should be individualized for each patient. Therapy should not be continued if epiphyseal fusion has occurred. Response to growth hormone therapy tends to decrease with time. However, failure to increase growth rate, particularly during the first year of therapy, suggests the need for close assessment of compliance and evaluation of other causes of growth failure, such as hypothyroidism, undernutrition, and advanced bone age.

Growth Hormone Deficiency (GHD)
A weekly dosage of up to 0.30 mg/kg (approximately 0.90 kU/kg) of body weight divided into daily subcutaneous injections is recommended.

Chronic Renal Insufficiency (CRI)
A weekly dosage of up to 0.35 mg/kg (approximately 1.05 kU/kg) of body weight divided into daily subcutaneous injections is recommended.

Nutropin AQ therapy may be continued up to the time of renal transplantation.

In order to optimize therapy for patients who require dialysis, the following guidelines for injection schedule are recommended:

1. Hemodialysis patients should receive their injection at night just prior to going to sleep or at least 3-4 hours after their hemodialysis to prevent hematoma formation due to the heparin.

2. Chronic Cycling Peritoneal Dialysis (CCPD) patients should receive their injection in the morning after they have completed dialysis.

3. Chronic Ambulatory Peritoneal Dialysis (CAPD) patients should receive their injection at the evening at the time of the overnight exchange.

Turner Syndrome
A weekly dosage of up to 0.375 mg/kg (approximately 1.125 kU/kg) of body weight divided into equal doses 3 to 7 times per week by subcutaneous injection is recommended.

ADMINISTRATION
The solution should be cleared immediately after removal from the refrigerator. Occasionally, after refrigeration, you may notice that small colorless particles of protein are present in the solution. This is unusual for solutions containing protein. Allow the vial to come to room temperature and gently swirl. If the solution is cloudy, the contents MUST NOT be injected.

Before needle insertion, wipe the top of the Nutropin AQ® (somatropin (DNA origin) injection) vial with rubbing alcohol or an antiseptic solution to prevent contamination of the contents by microorganisms that may be introduced by repeated needle insertions. It is recommended that Nutropin AQ be administered using sterile, disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy.

STABILITY AND STORAGE
Vial contents are stable for 28 days after initial use when stored at 2-8°C/36-46°F (under refrigeration). Avoid freezing the product of Nutropin AQ.

HOW SUPPLIED
Nutropin AQ is supplied as 10 mg (approximately 30 IU) of sterile liquid somatropin per vial.

Each carton contains six single vial cartons containing one 2 ml vial of Nutropin AQ® (somatropin (DNA origin) injection) (5 mg/mL). NDC 50927-114-11

Nutropin AQ® (somatropin (DNA origin) injection) manufactured by:

Genentech, Inc.

400 Port San Bruno Boulevard
South San Francisco, CA 94080-4990

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Revised March, 1997
**DESCRIPTION**

Nutropin AQ® (somatropin [rDNA origin] injection), is a human growth hormone (hGH) produced by recombinant DNA technology. Nutropin AQ has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of pituitary-derived human growth hormone. The protein is synthesized by a specific laboratory strain of E. coli as a precursor consisting of the hGH molecule preceded by the signal sequence found at an E. coli cell protein. This precursor is directly cleaved at the point of the signal peptide and the mature protein is secreted into the periplasm so that the protein is folded appropriately as it is synthesized.

Nutropin AQ is a highly purified preparation. Biological potency is determined by measuring the increase in body weight induced in hypophysectomized rats. Nutropin AQ is not more than 1.25 times that of pituitary-derived growth hormone of expiration. The dosedemated form of growth hormone has been extensively characterized and has been shown to be safe and fully active.

**CLINICAL PHARMACOLOGY**

**General**

In vitro and in vivo, pharmacological and clinical testing have demonstrated that Nutropin AQ is therapeutically equivalent to pituitary-derived human growth hormone. Treatment of patients who lack adequate endogenous growth hormone secretion, patients with clinical renal insufficiency, and patients with Turner syndrome that were treated with Nutropin AQ resulted in an increase in growth rate and an increase in insulin-like growth factor-I levels similar to that seen with pituitary-derived human growth hormone.

**Actions that have been demonstrated for Nutropin AQ, somatropin and/or pituitary-derived human growth hormone include:**

- **A. Tissue Growth:** 1. Skeletal Growth. Nutropin AQ stimulates skeletal growth in patients with growth failure due to a lack of adequate secretion of endogenous growth hormone or secondary to chronic renal insufficiency and in patients with Turner syndrome. In children, growth plate height at the ends of the long bones and metabolism of epiphyseal plate cells are directly stimulated by growth hormone and one of its mediators, insulin-like growth factor-1. Serum levels of insulin-like growth factor-1 are low in children and adolescents who are growth hormone deficient. Clinical experience with two controlled studies in boys and girls was considered as the evidence for treatment to growth hormone. These results in linear growth until these growth plates fuse at the end of puberty. 2. Cell Growth: Treatment with human growth hormone results in an increase in both the number of the liver and the size of skeletal muscle cells. 3. Organ Growth: Growth hormone of human pituitary origin influences the size of internal organs, including kidneys, and increases red cell mass. Treatment of hypopituitarism or growth dwarf rats with somatropin results in organ growth that is proportional to the increase in body growth. In normal subjects in nephropathy-induced uremia, somatropin promoted skeletal and body growth.

- **B. Protein Metabolism:** Linear growth is facilitated in part by growth hormone-stimulated protein synthesis. This is reflected by nitrogen retention and as demonstrated by a decline in urinary nitrogen excretion and blood urea nitrogen concentration during growth hormone therapy.

- **C. Carbohydrate Metabolism:** Growth hormone is a modulator of carbohydrate metabolism. For example, patients with inadequate or subnormal secretion of growth hormone sometimes experience hypoglycemia that is improved by treatment with growth hormone. Growth hormone therapy may decrease insulin sensitivity. Untreated patients with clinical renal insufficiency or Turner syndrome have an increased incidence of glucose intolerance. Administration of human growth hormone to normal adults or patients with growth hormone deficiency, chronic renal insufficiency, or Turner syndrome resulted in increases in mean serum fasting and postprandial insulin levels, although mean values remained in the normal range. In addition, mean fasting and postprandial glucagon and hemoglobin A1c levels remained in the normal range.

- **D. Lipid Metabolism:** Acute administration of pituitary-derived human growth hormone to humans results in lipid mobilization. Hereafter fatty acids increased in plasma within two hours of pituitary-derived human growth hormone administration. In growth hormone deficient patients, long-term growth hormone administration often decreases body fat. Mean cholesterol levels decreased in patients treated with Nutropin AQ® (somatropin [rDNA origin] injection).

- **E. Mineral Metabolism:** The retention of total body potassium in response to growth hormone administration apparently results from cellular growth. Serum levels of inorganic phosphorus may increase slightly in patients with inadequate secretion of growth hormone, chronic renal insufficiency, or in patients with Turner syndrome after growth hormone therapy due to metabolic activity associated with bone growth as well as increased turnover of phosphorus by the kidney. Serum calcium is not significantly altered in these patients. Sodium retention also occurs.

- **F. Connective Tissue Growth:** Growth hormone stimulates the synthesis of collagend and collagen as well as the urinary excretion of hydroxyproline.

**Pharmacokinetics**

Subcutaneous absorption—The absolute bioavailability of recombinant human growth hormone (rGH) after subcutaneous administration in healthy adult males has been determined to be 61% ± 2%. The mean terminal t1/2 after subcutaneous administration is significantly longer than that seen after intravenous administration (0.2 ± 0.7 vs. 19.5 ± 3.1 min) indicating that the subcutaneous absorption of the compound is slow and rate-limiting.

**Distribution—**Animal studies with rGH showed that growth hormone localizes to highly perfused organs, particularly the liver and kidneys. The distribution of steady state rGH in healthy adult males is about 50 mL/mg body weight, approximating the volume of serum.

**Metabolism—**Both the liver and kidneys have been shown to be important metabolizing organs for phytod-derived growth hormone. Animal studies suggest that the kidney is the dominant organ of clearance. Growth hormone is filtered at the glomerulus and reabsorbed in the proximal tubules. It is then cleared without reaching its constituent amino acids, which return to the systemic circulation.

**Elimination—**The mean terminal t1/2 after intravenous administration of rGH in healthy adult males is estimated to be 19.5 ± 3.1 min. Under these circumstances, 95% of the dose is eliminated in urine and feces. Measurement of rGH in healthy adult males is reported to be in the range of 116-174 mIU/mL.

**Bone Response of Formulations—Nutropin AQ® (somatropin [rDNA origin] injection) has been determined to be equivalent to the commercial formulations of rGH for injection based on the statistical evaluation of AUC and Cmax.

**Special Populations**

Pediatrics—Available literature data suggest that rGH clearances are similar in adults and children.

Gender—No data are available for adequately administered rGH. Available data for methionyl recombinant growth hormone, pituitary-derived growth hormone, and endogenous growth hormone (GH) suggest no consistent gender-related differences in GH clearance.

**Race—**Reported values for half-lives for endogenous GH in normal adult black males are not different from observed values for white males. No data are available for other races.

**Growth Hormone Deficiency (GHD)—**Reported values for clearance of GH in adults and children with GHD range from 138-274 mL/min and are similar to those observed in healthy adults and children. Mean terminal t1/2 values follow:

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* A: GH age ≤14 yr; B: GH age ≤14 yr; C: GH age >14 yr; M: GH at onset ≤14 yr.

**INDICATIONS AND USAGE**

Nutropin AQ® (somatropin [rDNA origin] injection) is indicated for the long-term treatment of growth failure due to a lack of adequate endogenous growth hormone secretion.

Nutropin AQ® (somatropin [rDNA origin] injection) is also indicated for the treatment of growth delay associated with chronic renal insufficiency.