

Document Information Page

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DFS Key Words:

Notes: SLR to add aluminum content language to package insert and vial label.

Linking Instructions: If this is the first action on the application, link the outgoing letter to the initial submission, RS, AR, or FO coded incoming document for the supplement being acted on, as appropriate. Otherwise, the outgoing letter must be linked to the major amendment submitted in response to the previous action letter.
In addition, the outgoing document should also be linked to all associated amendments and correspondences included in the action.

END OF DOCUMENT INFORMATION PAGE

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NDA 18-961/S-012

Abbott Laboratories
Attention: Jean Kirkeleit Davis
Manager, HPD Regulatory Affairs
200 Abbott Park Road, D389, J45
Abbott Park, IL 60064-6157

Dear Ms. Davis:

Please refer to your supplemental new drug application dated August 22, 2001, received August 24, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Chromic Chloride Injection, USP, 4 mcg/mL.

We acknowledge receipt of your submission dated February 15, 2002.

This supplemental new drug application provides for the addition of an aluminum toxicity statement to the WARNINGS section of the package insert and a maximum aluminum content statement to the vial label as required by 21 CFR 201.323.

PACKAGE INSERT (Plastic Vial)

The following have been added as the third and fourth paragraphs to the **WARNINGS** section:

WARNING: *This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.*

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

VIAL LABEL (Plastic Vial)

The following sentence was added after "See insert,"

"Contains no more than 100 micrograms/Liter of aluminum."

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted February 15, 2002 (marked up ID# 58-6220-R4 Rev. July 2001) and immediate container label submitted August 22, 2001 (ID# 58-2139-2/R4 – 7/01).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-961/S-012." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.

Director

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

pass through the plastic container wall will not significantly alter the drug concentration.

CLINICAL PHARMACOLOGY

Trivalent chromium is part of glucose tolerance factor, an essential activator of insulin-mediated reactions. Chromium helps to maintain normal glucose metabolism and peripheral nerve function.

Providing chromium during TPN helps prevent deficiency symptoms including impaired glucose tolerance, ataxia, peripheral neuropathy and a confusional state similar to mild/moderate hepatic encephalopathy.

Serum chromium is bound to transferrin (siderophilin) in the beta globulin fraction. Typical blood levels for chromium range from 1 to 5 mcg/liter, but blood levels are not considered a meaningful index of tissue stores. Administration of chromium supplements to chromium-deficient patients can result in normalization of the glucose tolerance curve from the diabetic-like curve typical of chromium deficiency. This response is viewed as a more meaningful indicator of chromium nutriture than serum chromium levels.

Excretion of chromium is via the kidneys, ranging from 3 to 50 mcg/day. Biliary excretion via the small intestine may be an ancillary route, but only small amounts of chromium are believed to be excreted in this manner.

INDICATIONS AND USAGE

Chromium 4 mcg/mL (Chromic Chloride Injection, USP) is indicated for use as a supplement to intravenous solutions given for total parenteral nutrition (TPN). Administration

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potential of Chromium 4 mcg/mL (Chromic Chloride Injection, USP) have not been performed, nor have studies been done to assess mutagenesis or impairment of fertility.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Chromium 4 mcg/mL (Chromic Chloride Injection, USP) is administered to a nursing woman.

Pediatric Use

See DOSAGE and ADMINISTRATION section. Safety and effectiveness in children have not been established.

Pregnancy Category C. Animal reproduction studies have not been conducted with chromic chloride. It is also not known whether chromic chloride can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Chromic chloride should be given to a pregnant woman only if clearly indicated.

ADVERSE REACTIONS

None known.

DRUG ABUSE AND DEPENDENCE

None known.

OVERDOSAGE

Trivalent chromium administered intravenously to TPN patients has been shown to be nontoxic when given at dosage levels of up to 250 mcg/day for two consecutive weeks.

Reported toxic reactions to chromium include nausea,

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helps to maintain chromium serum levels and to prevent depletion of endogenous stores and subsequent deficiency symptoms.

CONTRAINDICATIONS

None known.

WARNINGS

Direct intramuscular or intravenous injection of Chromium 4 mcg/mL (Chromic Chloride Injection, USP) is contraindicated, as the acidic pH of the solution may cause considerable tissue irritation.

Severe kidney disease may make it necessary to reduce or omit chromium and zinc doses because these elements are primarily eliminated in the urine.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

General

Do not use unless solution is clear and seal is intact. Chromium 4 mcg/mL (Chromic Chloride Injection, USP)

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vomiting, ulcers of the gastrointestinal tract, renal and hepatic damage, convulsions and coma. The acute LD₅₀ for intravenous trivalent chromium in rats was reported as 10 to 18 mg/kg.

DOSAGE AND ADMINISTRATION

Chromium 4 mcg/mL (Chromic Chloride Injection, USP) contains 4 mcg chromium/mL and is administered intravenously only after dilution. The additive should be administered in a volume of fluid not less than 100 mL. For the adult receiving TPN, the suggested additive dosage is 10 to 15 mcg chromium/day (2.5 to 3.75 mL/day). The metabolically stable adult with intestinal fluid loss may require 20 mcg chromium/day (5 mL/day), with frequent monitoring of blood levels as a guideline for subsequent administration. For pediatric patients, the suggested additive dosage is 0.14 to 0.20 mcg/kg/day (0.035 to 0.05 mL/kg/day).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See PRECAUTIONS.

HOW SUPPLIED

Chromium 4 mcg/mL (Chromic Chloride Injection, USP) is supplied in 10 mL Plastic Vials (List No. 4093).

Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP).

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ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

should only be used in conjunction with a pharmacy directed admixture program using aseptic technique in a laminar flow environment; it should be used promptly and in a single operation without any repeated penetrations. Solution contains no preservatives; discard unused portion immediately after admixture procedure is completed.

In assessing the contribution of chromium supplements to maintenance of glucose homeostasis, consideration should be given to the possibility that the patient may be diabetic.

Geriatric Use

An evaluation of current literature revealed no clinical experience identifying differences in response between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Laboratory Tests

Because chromium is present in the bloodstream in microgram quantities, routine measurement is impractical. If necessary, samples can be sent to a reference laboratory for assay.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic

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CHROMIUM 4 mcg/mL Chromic Chloride Injection, USP

FOR I.V. USE ONLY AFTER DILUTION

Plastic Vial

Rx only

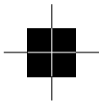
DESCRIPTION

Chromium 4 mcg/mL (Chromic Chloride Injection, USP) is a sterile, nonpyrogenic solution intended for use as an additive to intravenous solutions for total parenteral nutrition (TPN). Each mL of solution contains 20.5 mcg chromic chloride, hexahydrate and 9 mg sodium chloride. The solution contains no bacteriostat, antimicrobial agent, or added buffer. The pH is 2.0 (1.5 to 2.5); product may contain hydrochloric acid and/or sodium hydroxide for pH adjustment. The osmolarity is 0.308 mOsm/mL (calc.).

Chromic Chloride, USP is chemically designated chromic chloride, hexahydrate CrCl₃ • 6H₂O, a crystalline compound soluble in water.

Sodium Chloride, USP is chemically designated NaCl, a white, crystalline compound freely soluble in water.

The semi-rigid vial is fabricated from a specially formulated polyolefin. It is a copolymer of ethylene and propylene. The safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers. The small amount of water vapor that can



10 mL Vial

CHROMIUM
4 mcg/mL

Chromic Chloride Inj., USP

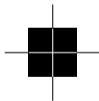
ABBOTT LABORATORIES, N. CHICAGO, IL 60064, USA

Rx only

NDC 0074-4093-01

FOR I.V. USE ONLY AFTER DILUTION.

Each mL contains chromic chloride, hexahydrate 20.5 mcg; sodium chloride 9 mg. 0.308 mOsmol/mL (calc).
Usual dosage: See insert. Contains no more than 100 micrograms/Liter of aluminum. 58-2139-2/R4-7/01



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/s/

Mary Parks
4/24/02 12:32:26 PM
for Dr. Orloff