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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
The letter begins on the next page.
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
It is also not known whether chromic chloride can cause harm to the unborn child. Studies in laboratory animals have not been conducted to determine whether Chromic Chloride Injection, USP is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, this product should not be administered to a nursing woman.


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 nutrition than serum chromium levels.

Excretion of chromium is via the kidneys, ranging from 3 to 50 mcg/day. Bilary 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 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) 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 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 chronic 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, 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).

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA
CHROMIUM
4 mcg/mL
Chromic Chloride Inj., USP
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.

Abbott Packaging
Graphics Art
LIST NO. 4093
COMMND. NO. 58-2139
LCRN 24166
DATE 6-9-00
LABEL EDITOR Van Sant
DATE PREPARED 7/30/01
STUDIO REFERENCE DB 5706-03
ARTIST SW/SW
FORMULA and LABEL CONTROL D-39B, APPROVAL
APPROVED BY
DATE
*NOT VALID UNLESS FINAL PROOFS CARRY D-39B APPROVAL SIGNATURE
COLOR
PMS Black
PMS 252
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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