ZINC INJECTABLE A 1MG/ML, SOLUTION INJECTABLE POUR PERFUSION-
zinc injection, solution
Laboratoire Aguettant

Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click here.

ZINC INJECTABLE A 1mg/ml, solution injectable pour perfusion

Dear Healthcare Provider Letter

Laboratoire AGUETTANT 1 Rue Alexander Fleming 69007 LYON - FRANCE

IMPORTANT DRUG INFORMATION

ZINC INJECTION AVAILABILITY

July 23, 2013

Subject: Temporary importation of Zinc injectable 1 mg/ml (zinc gluconate trihydrate) solution for infusion (equivalent to elemental zinc 1 mg/mL)

Dear Healthcare Professional,

Due to the current critical shortage of zinc injection drug products in the United States (U.S.), Laboratoire Aguettant (Aguettant) is coordinating with the Food and Drug Administration (FDA) to increase the availability of these products. Aguettant has initiated temporary importation into the U.S., through its U.S. distributor Baxter Healthcare Corporation, the non-FDA-approved zinc-containing drug, **Zinc injectable 1 mg/mL (zinc gluconate trihydrate) solution for infusion (equivalent to elemental zinc 1 mg/mL)**: Lot T-7506C, expiration date 02-2015, and Lot T-7519C, expiration date 03-2015.This product is marketed in France, and is manufactured for Aguettant at a FDA-inspected facility in France that is in compliance with Good Manufacturing Practices (GMP) regulations enforced in Europe.

At this time, FDA's regulatory discretion for the importation and distribution of Aguettant's **Zinc injectable 1 mg/mL (zinc gluconate trihydrate) solution for infusion** (**equivalent to elemental zinc 1 mg/mL**) is limited to Aguettant and its distributor Baxter Healthcare Corporation during the critical shortage of zinc injection. Importation and distributionof this product in the United States byany entity other than Aguettant and its distributor Baxter Healthcare Corporation is outside the scope of FDA's regulatory discretion, and FDA has not approved Aguettant's Zinc injectable product in the U.S.

Effective immediately, and during this temporary period, Aguettant will offer the following presentation of zinc injection:

Zinc Injectable (zinc gluconate trihydrate) 1 mg/mL, solution for infusion	
10 mL glass vials	Authorization# 333 414-4 (France) Box of 10 vials

The vial and carton labels will display the original French product labels as marketed inFrance. At the end of this letter is a product comparison table with the French prescribing information translated into English, as well as images of the French labels with their English translation for your reference.

Zinc injectable 1 mg/mL (zinc gluconate trihydrate) solution for infusion is meant to be used the same way as the U.S. marketed drugs, and provides **1 mg/mL of elemental zinc**. Each vial is **single**

use only and **must be diluted prior to infusion**. Please discard each vial after single use.

There are some key differences in labeling between the FDA-approved zinc injection drug product and Aguettant's zinc injectable 1 mg/mL (zinc gluconate trihydrate) solution for infusion (please see also the product comparison tables attached).

- **Zinc injectable 1 mg/mL solution for infusion (equivalent to elemental zinc 1 mg/mL)** contains **zinc gluconate trihydrate** as the active substance, which is a different salt than those used in other zinc drugs for injection, i.e. zinc chloride and zinc sulfate. Also, note that our manufacturer of zinc gluconate trihydrate complies with the U.S. Pharmacopoeia monograph for zinc gluconate trihydrate. We consider this formulation an appropriate alternative to the FDA-approved zinc injection drug product when used as explained below.
- The composition in active substance is equivalent to one milligram of elemental zinc per milliliter of solution. The only excipient is water for injections, and the pH of the drug is comprised between 5.5 and 7.0.
- No specific precautions are required for the storage of Zinc injectable 1 mg/mL (zinc gluconate trihydrate) solution for infusion. **As with your usual zinc injection drug products, you may store this at controlled room temperature 20°C to 25°C (68°F to 77°F).**

Zinc injectable 1 mg/mL (zinc gluconate trihydrate) solution for infusion is available only by prescription in theU.S.

Please refer to the package insert for the FDA-approved zinc injection drug product for full prescribing information and follow the instructions presented in the FDA-approved package insert for dosing and use in pregnancy recommendations. Please note the difference in the maximum potential aluminum content (higher in the foreign product).

- Zinc injectable 1 mg/mL (zinc gluconate trihydrate), solution for infusion is meant to be used by parenteral administration (infusion), **only after dilution** in an isotonic solution or in a mixture for parenteral nutrition.
- **Dosing instructions** for Zinc injectable 1 mg/mL (zinc gluconate trihydrate), solution for infusion differ from dosing instructions for the FDA-approved zinc injection drug product. We recommend that you follow the labeling instructions for the FDA-approved zinc injection drug product.
- **Instructions regarding use in pregnancy** for Zinc injectable 1 mg/mL (zinc gluconate trihydrate), solution for infusion differ from dosing instructions for the FDA-approved zinc injection drug product. We recommend that you follow the labeling instructions for the FDA-approved zinc injection drug product.
- **Maximum potential aluminum content** for Zinc injectable 1 mg/mL (zinc gluconate trihydrate), solution for infusion is higher than that for the FDA-approved zinc injection drug product. Consider risks of aluminum toxicity against benefit of zinc supplementation when prescribing Zinc injectable 1 mg/mL (zinc gluconate trihydrate), solution for infusion.

The aluminum content of Lot T-7506C and Lot T-7519C is each no more than 100 mcg/L at the time of this import. Aluminum testing is not a requirement for registration of this product inFrance. However in support of FDA's regulatory discretion for temporary importation, testing was performed perU.S.regulation 21 CFR 201.323. The aluminum content for lots at expiry was found to be no higher than 350 mcg/L.

The barcodemay not registeraccurately on the U.S. scanning systems. Institutions should manually input the product into their systems and confirm that barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

To place an order, or if you have any questions about the information contained in this letter or the use of Zinc injectable 1 mg/mL (zinc gluconate trihydrate) solution for infusion, please call **Baxter's Center for Service at 1-888-229-0001**, available from 7:00 am to 6:00 pm Central Standard Time, or

email CFS_Customer_Service@baxter.com.

We encourage health care providers to report any adverse events and medication errors that occur while using this product, as for any other drug. To report adverse events associated with Zinc injectable 1 mg/mL (zinc gluconate trihydrate) solution for infusion, please call **Baxter Healthcare Surveillance at 1-866-888-2472 (**Monday – Friday 9:00 am to 5:00 pm Central Standard Time), or fax at 1-800-759-1801 (24 hrs/day, 7 days/week).

Adverse events that may be related to the use of this product may also be reported to FDA's MedWatch Adverse Event Reporting Program either online, by regular mail or by fax:

- Online: http://www.fda.gov/medwatch/report.htm
- Regular mail: Use postage paid FDA form 3500 available at :

http://www.fda.gov/medwatch/getforms.htm

Mail to MedWatch FDA,5600 Fishers Lane,Rockville,MD20852-9787

- Fax: 1-800-FDA-0178

We remain at your disposal to answer the questions you might have about our product, and provide more information if needed.

Thank you for your understanding,

Eric ROUGEMOND, MD CEO of Laboratoire Aguettant

Product comparison tables

	ZINC 1 mg/ml zinc chloride injection, USP FDA-approved zinc injection drug product	**Zinc injectable 1 mg/ml, solution for infusion** ***(translated into English)*** Laboratoire Aguettant
Composition		
Active ingredient	Zinc Chloride, USP	Zinc Gluconate, USP
Strength	2.09 mg/mL zinc chloride equivalent to **1 mg/mL elemental zinc**	7.80 mg/mL zinc gluconate **equivalent to 1 mg/mL elemental zinc**
Inactive ingredients	Sodium chloride 9 mg/mL Hydrochloric acid or sodium hydroxide for pH adjustment	Water for injections
Content in aluminum	Not more than 150 mcg/L	Not more than 1500 mcg/L *(not stated on the insert)*
Physiochemical parameters		
pH	2.0 (1.5 to 2.5)	5.5 to 7.0 *(not stated on the insert)*
Osmolarity	0.354 mOsmol/mL (calc.)	0.30 to 0.35 mOsmol/mL *(not stated on the insert)*
Description	Sterile, non-pyrogenic solution intended for use as an additive to intravenous solutions for total parenteral nutrition (TPN). The solution contains no bacteriostat, antimicrobial agent or added buffer.	Solution for infusion. Supplementation solution for prolonged parenteral nutrition and for prevention of severe zinc deficiency. Sterile solution *(not stated on the insert)* The solution contains no bacteriostat, antimicrobial agent or added buffer.

		(not stated on the insert)
How supplied	10 mL plastic vials	10 mL glass vials; pack of 10 vials
Storage conditions	Store at 20 to25°C(68 to77°F). [See USP Controlled Room Temperature.]	No special precautions for storage.
Country-specific information		Marketing Authorization Number: 333 414-4
Expiration date format		MM/YYYY
Drug status	Rx only	Non-prescription drug
Authorization holder		Laboratoire AGUETTANT 1, rue Alexander Fleming 69007 LYON FRANCE

Comparison of prescribing information		
Clinical pharmacology *5.1 Pharmacodynamic properties* *5.2 Pharmacokinetic properties* *5.3 Preclinical safety data*	Zinc is an essential nutritional requirement and serves as a cofactor for more than 70 different enzymes including carbonic anhydrase, alkaline phosphatase, lactic dehydrogenase, and both RNA and DNA polymerase. Zinc facilitates wound healing, helps maintain normal growth rates, normal skin hydration, and the senses of taste and smell. Zinc resides in muscle, bone, skin, kidney, liver, pancreas, retina, prostate and particularly in the red and white blood cells. Zinc binds to plasma albumin, a2-macroglobulin, and some plasma amino acids including histidine, cysteine, threonine, glycine, and asparagine. Ingested zinc is excreted mainly in the stool (approximately 90%), and to a lesser extent in the urine and in perspiration. Providing zinc helps prevent development of deficiency symptoms such as: Parakeratosis, hypogeusia, anorexia, dysosmia, geophagia, hypogonadism, growth retardation and hepatosplenomegaly. The initial manifestations of hypozincemia in TPN are diarrhea, apathy and depression. At plasma levels below 20 mcg zinc/100 mL dermatitis followed by alopecia has been	**5.1 Pharmacodynamic properties** **INTRAVENOUS SOLUTIONS** (B: BLOOD AND BLOOD FORMING ORGANS) Zinc is an essential component of at least 120 metalloenzymes including carbonic anhydrases, alkaline phosphatases, carboxypeptidases, oxidoreductases, transferases, ligases, hydrolases, isomerases and alcohol dehydrogenases. Zinc also has an important role in the synthesis of nucleic acids (DNA and RNA) and in the regulation of RNA catabolism. Zinc is involved in the transformation of T-lymphocytes and might be involved in the synthesis of insulin. Hence, zinc

	reported for TPN patients. Normal zinc plasma levels are 100 ± 12 mcg/100 mL.	participates in the metabolism of carbohydrates, lipids and proteins. Zinc is indispensable for the growth of premature and full term infants and children. **5.2 Pharmacokinetic properties** Not available. **5.3 Preclinical safety data** Not available.
Indications and usage *4.1 Therapeutic indications*	Zinc 1 mg/mL (Zinc Chloride Injection, USP) is indicated for use as a supplement to intravenous solutions given for TPN. Administration helps to maintain zinc serum levels and to prevent depletion of endogenous stores, and subsequent deficiency symptoms.	Supplementation solution for prolonged parenteral nutrition and for prevention of severe zinc deficiency in conditions such as (but not limited to) severe denutrition, hypercatabolism, digestive fistula, chronic diarrhea. The supplementation scheme must cover the daily needs (3 to 4 mg zinc per day for adults) and compensate for abnormally high losses (up to 15 mg per day).
Contraindications *4.3 Contraindications*	None known.	Hypersensitivity to any of the ingredients.
Warnings	Direct intramuscular or intravenous injection of Zinc 1 mg/mL (Zinc Chloride Injection, USP) is contraindicated as the acidic pH of the solution (2) 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	**4.4 Special warnings and precautions for use** **<u>Warning</u>** This product must never be injected as is, but diluted in a solution for infusion. **4.5 Interaction with other medicinal products and other forms of interaction** In complex parenteral nutrition protocols

	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.	nutrition protocols, special precaution is required to avoid incompatibilities among the added medications.
Precautions *4.6 Pregnancy and lactation* *4.7 Effects on ability to drive and use machines* *6.2 Incompatibilities*	**General** Do not use unless the solution is clear and the seal is intact. Zinc 1 mg/mL (Zinc 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. Zinc should not be given undiluted by direct injection into a peripheral vein because of the likelihood of infusion phlebitis and the potential for increased excretory loss of zinc from a bolus injection. Administration of zinc in the absence of copper may cause a decrease in serum copper levels. **Laboratory Tests** Periodic determinations of serum copper as well as zinc are suggested as a guideline for subsequent zinc administration. **Carcinogenesis, Mutagenesis, and Impairment of Fertility** Long-term animal studies to evaluate the carcinogenic potential of Zinc 1 mg/mL (Zinc 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 Zinc 1 mg/mL (Zinc Chloride Injection, USP) is administered to a nursing woman. **Pediatric Use** See DOSAGE and ADMINISTRATION section. *Pregnancy Category C.* Animal reproduction studies have not been conducted with zinc chloride. It is also not known whether zinc chloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zinc chloride should be given to a pregnant woman only if clearly needed. **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.	**4.6 Pregnancy and lactation** Based on available data, it is possible to use this product for pregnant or breast-feeding women. **4.7 Effects on ability to drive and use machines** Not relevant. **6.2 Incompatibilities** In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Adverse reactions		Adverse effects are observed with high

reactions *4.8 Undesirable effects*	None known.	observed with high dosages (see section 4.9).
Drug abuse and dependence *(No equivalent section)*	None known.	
Overdosage *4.9 Overdose*	Single intravenous doses of 1 to 2 mg zinc/kg body weight have been given to adult leukemic patients without toxic manifestations. However, acute toxicity was reported in an adult when 10 mg zinc was infused over a period of one hour on each of four consecutive days. Profuse sweating, decreased level of consciousness, blurred vision, tachycardia (140/min), and marked hypothermia (94.2° F) on the fourth day were accompanied by a serum zinc concentration of 207 mcg/dl. Symptoms abated within three hours. Hyperamylasemia may be a sign of impending zinc overdosage; patients receiving an inadvertent overdose (25 mg zinc/liter of TPN solution, equivalent to 50 to 70 mg zinc/day) developed hyperamylasemia (557 to 1850 Klein units; normal: 130 to 310). Death resulted from an overdosage in which 1683 mg zinc was delivered intravenously over the course of 60 hours to a 72 year old patient. Symptoms of zinc toxicity included hypotension (80/40 mm Hg), pulmonary edema, diarrhea, vomiting, jaundice, and oliguria, with a serum zinc level of 4184 mcg/dl. Calcium supplements may confer a protective effect against zinc toxicity.	No overdose cases were reported with ZINC INJECTABLE 1mg/ml, solution for infusion. However, overdose cases by intravenous injection of zinc were reported with manifestations of acute toxicity such as profuse sweating, blurred vision, decreased level of consciousness, hypothermia, tachycardia, jaundice and pulmonary edema. Hyperamylasemia may be a sign of impending zinc overdosage. Calcium supplementation may confer a protective effect.
Dosage and administration *4.2 Posology and method of administration* *6.6 Special precautions for*	Zinc 1 mg/mL (Zinc Chloride Injection, USP) contains 1 mg zinc/mL and is administered intravenously only after dilution. The additive should be diluted prior to administration in a volume of fluid not less than 100 mL. For the metabolically stable adult receiving TPN, the suggested intravenous dosage is 2.5 to 4 mg zinc/day (2.5 to 4 mL/day). An additional 2 mg zinc/day (2 mL/day) is suggested for acute catabolic states. For the stable adult with fluid loss from the small bowel, an additional 12.2 mg zinc/liter of small bowel fluid lost (12.2 mL/liter of small bowel fluid lost), or an additional 17.1 mg zinc/kg of stool or ileostomy output (17.1 mL/kg of stool or ileostomy output) is recommended. Frequent monitoring of zinc blood levels is suggested for patients receiving more than the usual maintenance dosage	**4.2 Posology and method of administration** Each mL contains 1 mg of elemental zinc. The dosage must be adapted to each patient, taking into account losses and zinc status. The solution is a supplementation additive for parenteral nutrition intended to be used in mixtures for parenteral nutrition or diluted in isotonic solutions. Recommended daily intakes by intravenous route are the

precautions for disposal and other handling	level of zinc. For full term infants and children up to 5 years of age, 100 mcg zinc/kg/day (0.1 mL/kg/day) is recommended. For premature infants (birth weight less than 1500 g) up to 3 kg in body weight, 300 mcg zinc/kg/day (0.3 mL/kg/day) is suggested. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See PRECAUTIONS.	following: - In pediatric patients: - Premature infants: 0.3 to 0.35 mg zinc/kg/day, - Full term infants: 0.1 to 0.2 mg zinc/kg/day, - Children: 5 mg zinc/day. - In adults: 3 to 15 mg zinc/day. **6.6 Special precautions for disposal and other handling** No special precautions.

TRANSLATION OF FRENCH VIAL AND CARTON LABELS		
	Zinc injectable 1 mg/ml, solution for infusion ***Product will be distributed with the original French labels*** Laboratoire Aguettant	**Zinc injectable 1 mg/ml, solution for infusion** ***English translation – for information only*** ***Product will be distributed with the original French labels*** Laboratoire Aguettant
Carton Label		*(not stated on the label):* Please refer to the package insert for the FDA-approved zinc injection drug product (zinc chloride injection, 1 mg/mL) for full prescribing information.
Vial Label		*(not stated on the label):*Equivalent to elemental zinc 1 mg/mL.

Carton Label

ZINC INJECTABLE

Gluconate de zinc trihydraté

À 1 mg/ml, SOLUTION INJECTABLE POUR PERFUSION

Perfusion IV

10 flacons

10 mg
10 ml

AGUETTANT

ZINC INJECTABLE
Gluconate de zinc trihydraté
À 1 mg/ml, SOLUTION INJECTABLE POUR PERFUSION

Perfusion IV

10 flacons

10 mg
10 ml

Composition: Gluconate de zinc, 3 H_2O.....77,96 mg (soit 10 mg de zinc élément)
Eau pour préparations injectables..... q.s.p. .....10 ml pour un flacon

Forme pharmaceutique et contenu : Solution injectable pour perfusion.

Mode et voie d'administration : Perfusion IV.

Mise en garde spéciale : Ce produit ne doit en aucun cas être injecté pur mais dilué dans une solution perfusable isotonique ou en mélange avec des solutions de nutrition parentérale.

Indications d'utilisation : Ce médicament est une solution de supplémentation en nutrition parentérale dans les situations où une carence accentuée doit être redoutée : dénutrition avancée, hypercatabolisme, fistules digestives, diarrhées chroniques... La supplémentation doit couvrir les besoins et compenser les pertes anormalement élevées.

Lot :

EXP.:

NE PAS LAISSER À LA PORTÉE DES ENFANTS .

Médicament autorisé
N°333 414-4
ou 34009 333 414 4 2
UCD : 34008 912 938 5 2

340093334I442

5018458 09/10

AGUETTANT

Titulaire - Exploitant - Fabricant :
Laboratoire AGUETTANT - 1 rue A. Fleming - 69007 LYON - France

Via Label

ZINC INJECTABLE A 1MG/ML, SOLUTION INJECTABLE POUR PERFUSION

zinc injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:60710-001
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ZINC GLUCONATE TRIHYDRATE (UNII: F2F0XU34WQ) (ZINC CATION - UNII:13S1S8SF37)	ZINC CATION	1 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:60710-001-10	10 in 1 BOX	10/01/2013	
1		10 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Unapproved drug for use in drug shortage		10/01/2013	

Labeler - Laboratoire Aguettant (267584998)

Establishment

Name	Address	ID/FEI	Business Operations
Delpharm Tours		267589047	manufacture(60710-001)