

ADULT MULTI-TRACE ELEMENT AVAILABILITY

May 29, 2013

Dear Healthcare Professional,

Due to the critical shortage of adult multi-trace elements in the US market, Fresenius Kabi, USA LLC (Fresenius Kabi USA) is coordinating with the U.S. Food and Drug Administration (FDA) to provide an alternative treatment option during this critical shortage period.

At this time, FDA's regulatory discretion for the importation and distribution of FK USA's Addamel™ N 10 mL Concentrate for Infusion Single Dose Plastic Ampules is limited to Fresenius Kabi USA during the critical shortage of adult multi-trace elements. Importation or distribution of this product in the United States by any other entity is outside the scope of FDA's regulatory discretion, and FDA has not approved Fresenius Kabi's Addamel™ N product for marketing in the U.S.

Effective immediately, and during this temporary period, Fresenius Kabi USA will offer the following presentation of adult multi-trace elements:

Addamel N 10 mL Concentrate for Infusion Single Dose Plastic Ampule		
Trace Elements	Content of Trace Elements (per 1 mL)	Active Ingredient (per 1 mL)*
Zinc (Zn)	0.65 mg (10 µmol)	Zinc Chloride 1.36 mg
Copper (Cu)	0.13 mg (2 µmol)	Copper Chloride 0.34 mg
Manganese (Mn)	0.027 mg (0.5 µmol)	Manganese Chloride 0.099 mg
Chromium (Cr)	1 mcg (0.02 µmol)	Chromic Chloride 5.33 mcg
Selenium (Se)	3.2 mcg (0.04 µmol)	Sodium Selenite** 6.90 mcg
Iron (Fe)	0.11 mg (2 µmol)	Ferric Chloride 0.54 mg
Molybdenum (Mo)	1.9 mcg (0.02 µmol)	Sodium Molybdate** 4.85 mcg
Iodine (I)	0.013 mg (0.1 µmol)	Potassium Iodide** 16.6 mcg
Fluorine (F)	0.095 mg (5 µmol)	Sodium Fluoride** 0.21 mg
<p>*Active Ingredient content is information only and not to be used for dosing of the products. Use trace element content for dosing.</p> <p>**The total sodium and potassium content in Addamel N corresponds to 5.12 µmol of Sodium (Na) and 0.1 µmol of Potassium (K) per 1 mL.</p>		

It is important to note that there are some key differences in the formulation and labeling between the current U.S. marketed adult multi-trace element products and Addamel N that you need to be aware of which appear in the following table:

Property	Multi-Trace element products (U.S. product)	Addamel N
Trace elements & active ingredient salt forms present	4 or 5 trace elements present. (Depending on the product.) <u>These include:</u> zinc sulfate, cupric sulfate, manganese sulfate, chromic chloride & selenious acid	9 trace elements present. <u>These include:</u> zinc chloride, copper chloride, manganese chloride, chromic chloride, sodium selenite, ferric chloride, sodium molybdate, potassium iodide & sodium fluoride
Differences in amount of trace elements present in each 1 mL	See package insert	See package insert
Package	10 mL multi-dose vials 1 mL single dose vials	10 mL single dose ampule
Preservative	1 mL vials preservative free 10 mL vials preservative is present	10 mL ampule preservative free Strict Aseptic Technique must always be maintained during handling.
Contains Iron	No	Yes, Ferric Chloride. Addamel N can be added into dextrose/amino acid parenteral nutrition formulations. Addamel N has been tested in parenteral formulations available outside the U.S. containing IV fat emulsion under European standards with shown compatibility. Similar tests have not been done using U.S. products and methodology, thus caution should be taken when adding Addamel N to parenteral formulations containing IV fat emulsions due to potential disturbance interaction of the fat emulsion. Addamel N can be administered using standard IV fluids.
Indications and contraindications	See package insert	Addamel N is indicated in patients as a supplement in intravenous nutrition to meet basal to moderately increased requirements of trace elements. Addamel N is contraindicated in patients who have total biliary obstruction or known hypersensitivity to the active substance or to any of the excipients.
Barcode	Information not available	Any barcodes on Addamel N product will not be appropriately recognized by scanning systems used in the United States and should NOT be used. Institutions will have to manually input the product into their systems and confirm that barcode systems do not provide incorrect information when the product is scanned.
<p style="text-align: center;">For questions regarding Addamel N in the United States, please contact Fresenius Kabi USA Vigilance and Medical Affairs at 1-800-551-7176, Monday – Friday, between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com.</p>		

Indications:

- Addamel N is indicated as a supplement in intravenous nutrition of adults to meet the requirements of trace elements. Before administering Addamel N, the physician must assess the metabolic requirements for trace elements and disease state of the patient. Frequent determinations of serum levels of the various trace elements are suggested as a guideline for adjusting the dosage or completely omitting the solution.

Preparation / Administration:

- Addamel N must be diluted before administration and strict aseptic technique must always be maintained during handling. When additions are made to an infusion solution, the infusion should be completed within 24 hours from preparation to prevent microbiological contamination. The left over contents of opened bottles/vials/ampules should be discarded and not kept for later use.
- The trace elements present in the solution are physically compatible with the electrolytes and vitamins usually present in the amino acid/dextrose solution used for parenteral nutrition. Addamel N has been tested in parenteral formulations available outside the U.S. containing IV fat emulsion under European standards with shown compatibility. Similar tests have not been done using U.S. products and methodology, thus caution should be taken when adding Addamel N to parenteral formulations containing IV fat emulsions due to potential disturbance interaction of the fat emulsion.
- Addamel N can be administered using standard IV fluids.

Contraindications / Warnings:

- Addamel N is contraindicated in patients with total biliary obstruction. Addamel N should be used with caution in patients with impaired biliary and/or renal function when the excretion of trace elements may be significantly decreased and there is an increased risk for accumulation of trace elements. Addamel N should also be used with caution in patients with biochemical or clinical evidence of liver dysfunction (especially cholestasis). If treatment is continued for more than 4 weeks checking of manganese levels is required. In case of a chronic overload of iron there is a risk of hemosiderosis.
- Addamel N is not tested for aluminum. Aluminum can be toxic and may reach toxic levels with prolonged parenteral administration if kidney function is impaired.
- Allergic reactions to iodine may occur following topical application. No adverse reactions are known to occur as a consequence of using the recommended intravenous iodide dosage levels.
- The container closure is not made from natural rubber latex.
- Keep ampules in the outer carton to protect from light.

Refer to the package insert for full prescribing information for Addamel N

This communication and product information is available on the APP web site www.APPpharma.com and on the FDA Drug Shortage web site. <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>.

To report adverse events, quality problems or medication errors experienced with the use of Addamel N, call Fresenius Kabi USA Vigilance and Medical Affairs at 1-800-551-7176, Monday – Friday, between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com.



Fresenius Kabi USA CONTACT NUMBERS: Please use the following contact numbers as appropriate:

Reason To Call	Department	Number
ADE Reporting/Clinical/Technical Info.	Vigilance and Medical Affairs Dept.	1-800-551-7176
Product Availability & Ordering	Customer Service Department	1-888-386-1300

Adverse events may also be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- **Online:** www.fda.gov/medwatch/report.htm
- **Regular Mail:** use postage-paid FDA form 3500 available at: www.fda.gov/MedWatch/getforms.htm. Mail to MedWatch 5600 Fishers Lane, Rockville, MD 20852-9787
- **Fax:** 1-800-FDA-0178

Sincerely,

Melanie Power-Burns
Senior Director, U.S. Quality & Compliance

Adult Multi-Trace Element Comparison Table (per mL)

Trace Elements	A.S.P.E.N. Recommended Daily Adult Requirements*	Multitrace 4** & Multitrace 5** (per 1 mL)	Multitrace 4 Concentrate** & Multitrace 5 Concentrate** (per 1 mL)	Addamel N (per 1 mL)
Zinc (Zn)	2.5-5 mg	1 mg	5 mg	0.65 mg
Copper (Cu)	0.3-0.5 mg	0.4 mg	1 mg	0.13 mg
Manganese (Mn)	0.06-0.1mg	0.1 mg	0.5 mg	0.027 mg
Chromium (Cr)	10-15 mcg	4 mcg	10 mcg	1 mcg
Selenium (Se)	20-60 mcg	20 mcg	60 mcg	3.2 mcg
Iron (Fe)	Not routinely added in the U.S.	-	-	0.11 mg
Molybdenum (Mo)		-	-	1.9 mcg
Iodine (I)		-	-	0.013 mg
Fluorine (F)		-	-	0.095 mg

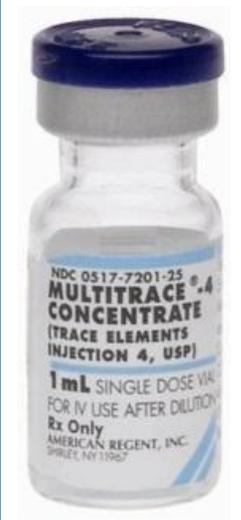
*Vanek V, Borum P, Buchman A, et al. A.S.P.E.N. Position Paper: Recommendation for Changes in Commercially Available Parenteral Multivitamin and Multi-Trace Element Products. *Nutr Clin Pract.* 2012; June: 1-52.

**Multitrace 4, Multitrace 5, Multitrace 4 Concentrate, Multitrace 5 Concentrate are registered products of American Regent.

Adult Active Ingredient Comparison Table

Trace Elements	Multitrace 4	Multitrace 5	Addamel N
Zinc (Zn)	Zinc Sulfate	Zinc Sulfate	Zinc Chloride
Copper (Cu)	Cupric Sulfate	Cupric Sulfate	Copper Chloride
Manganese (Mn)	Manganese Sulfate	Manganese Sulfate	Manganese Chloride
Chromium (Cr)	Chromic Chloride	Chromic Chloride	Chromic Chloride
Selenium (Se)	-	Selenious Acid	Sodium Selenite
Iron (Fe)	-	-	Ferric Chloride
Molybdenum (Mo)	-	-	Sodium Molybdate
Iodine (I)	-	-	Potassium Iodide
Fluorine (F)	-	-	Sodium Fluoride

Adult Label Product Comparison Table

	Multitrace 4	Multitrace 4 Concentrate		Multitrace 5	Multitrace 5 Concentrate		Addamel N
							
NDC#	0517-7410-25	0517-7201-25	0517-7210-25	0517-8510-25	0517-8201-25	0517-8210-25	63323-143-97
Fill Volume	10 mL	1 mL	10 mL	10 mL	1 mL	10 mL	10 mL
Description	Multiple Dose Vial	Single Dose Vial	Multiple Dose Vial	Multiple Dose Vial	Single Dose Vial	Multiple Dose Vial	Single Dose Plastic Ampule
Manufacturer	American Regent	American Regent	American Regent	American Regent	American Regent	American Regent	Fresenius Kabi Norge A/S
Preservative Free	No	Yes	No	No	Yes	No	Yes