NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ADDAVEN® (infusion, solution concentrate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL ampoule of Addaven contains:

Chromic chloride hexahydrate	53.33 µg
Cupric chloride dihydrate	1.02 mg
Ferric chloride hexahydrate	5.40 mg
Manganese chloride tetrahydrate	198 µg
Potassium iodide	166 µg
Sodium fluoride	2.10 mg
Sodium molybdate dihydrate	48.5 µg
Sodium selenite	173 µg
Zinc chloride	10.5 mg

The active ingredients per 10 mL of Addaven correspond to the following electrolyte profile:

Chromium (Cr^{3+})	0.20 µmol (10 µg)
Copper (Cu^{2+})	6.0 µmol (380 µg)
Iron (Fe^{3+})	20 µmol (1.10 mg)
Manganese (Mn^{2+})	1.0 µmol (55 µg)
Iodine (I^{-})	1.0 µmol (130 µg)
Fluoride (F^{-})	50 µmol (950 µg)
Molybdenum (Mo^{6+})	0.20 µmol (19 µg)
Selenium (Se^{4+})	1.0 µmol (79 µg)
Zinc (Zn^{2+})	77 µmol (5.0 mg)

The content of sodium and potassium correspond to:

Sodium content:	52 µmol (1.20 mg)
Potassium content:	1 µmol (39 µg)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Addaven is a concentrated trace element solution for infusion which is clear and colourless to slightly yellow.

Osmolality:	3100 mOsm/kg water
pH:	2.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To meet basal to moderately increased requirements of trace elements in parenteral nutrition in adults and children weighing 15 kg and over, when either oral or enteral nutrition is inappropriate

4.2 Dose and method of administration

Dosage

Adults: The recommended daily dosage of Addaven in adult patients with basal to moderately increased requirements is 10 mL (one ampoule).

In patients with renal or hepatic impairments, or mild cholestasis the dose should be adapted.

Children ≥ 15kg: 0.1 mL Addaven is given per kg body weight and day.

Method of administration
Addaven must not be given undiluted. Addaven shall be diluted in a parenteral nutrition solution/emulsion before being given as an intravenous infusion.

Information on admixtures is available upon request.

Longer infusion periods are desirable, as this will minimise renal losses. The typical minimum infusion time when Addaven is administered as part of parenteral nutrition is 8 hours.

Product is for single use in one patient only. Discard any residue.

Compatibility
Only medicinal products and nutrition solutions where compatibility has been documented may be added to Addaven. Addaven is used as an additive to parenteral nutrition admixtures in compounded bags where data are available. Compatibility data are available for the addition of 10 mL Addaven to the named branded products SMOFlipid, Intralipid 20%, Aminoven 10%, Vamin 18 EF, Dipeptiven, Soluvit N, Vitalipid N Adult and Glycophos in defined amounts and generics of glucose and electrolytes in defined concentrations. 10 mL of Addaven can also be added to the SmofKabiven and Kabiven range of products.

NOTE: Addaven should never be added directly to a lipid emulsion because of the destabilising effects of trace elements. It is recommended that the macronutrients (amino acid solution and glucose with or without lipid emulsion) are mixed first, before adding the Addaven and any further additions, e.g. vitamins or electrolytes. Additions should be made aseptically.

4.3 Contraindications
- Hypersensitivity to the active substances or to any of the excipients.
- Conditions with total biliary obstruction.
- Wilson's disease, hemochromatosis.
- Children less than 15 kg body weight

4.4 Special warnings and precautions for use
Parenterally administered iron or iodine preparations can cause hypersensitivity reactions on rare occasions, including serious and potentially fatal anaphylactic reactions.

Patients should be clinically observed for signs and symptoms of hypersensitivity reactions. In case of hypersensitivity reactions, the infusion should be stopped immediately and appropriate measures performed.

If iron is taken orally in parallel with infusion of Addaven, the total intake of iron should be determined to ensure that there is no iron accumulation.

Peripheral infusion of Addaven diluted in saline or glucose instead of a parenteral nutrition solution may result in local intolerability due to low pH. Osmolarity also needs to be considered.

Addaven should be used with caution in patients with liver dysfunction. Liver dysfunction, including impaired biliary excretion, may interfere with excretion of trace elements from Addaven, leading to a risk of accumulation.

Addaven should be used with caution in patients with impaired renal function as excretion of some trace elements in urine may be significantly decreased.

Monitoring of trace element levels, especially manganese, is recommended.

If an individual patient has a markedly increased requirement for any of the trace elements, the regimen can be adjusted using separate supplements.

Laboratory and some animal studies indicate that vitamin B6 deficiency can increase the production of oxalate from xylitol. Adequate levels of vitamin B6 should be maintained.

Paediatric use
Addaven is not recommended for use in children less than 15 kg body weight.

Use in the elderly
Because of the increased likelihood of impaired renal or hepatic function or concomitant disorders and their treatment, Addaven should be used with cautious monitoring in the elderly.

Genotoxicity
Studies with Addaven have not been performed to evaluate the genotoxic potential.

Carcinogenicity
Studies with Addaven have not been performed to evaluate the carcinogenic potential.

Effects on laboratory tests
No effects on laboratory tests have been identified. Addaven is administered as part of parenteral nutrition.

4.5 Interactions with other medicines and other forms of interaction
Molybdenum interacts with copper to form complexes that increase urinary elimination of copper.
Amino acids, which are present in all total IVN mixtures, could complex with zinc and copper and the complex could be excreted in urine. However, amino acid loss in urine is usually small.
Interactions of copper with ascorbic acid from vitamin supplementation of the parenteral nutrition mixture may occur, resulting in oxidative loss of ascorbic acid, which can be limited by use of oxygen impermeable bags.

4.6 Fertility, pregnancy and lactation
Fertility
The potential effects of Addaven on fertility and general reproductive performance have not been determined.

Pregnancy
Animal reproduction studies or clinical investigations during pregnancy have not been carried out with Addaven.

Breast-feeding
The active substances in Addaven are secreted in human milk and effects have been shown in breastfed newborns/infants of treated women. These effects are desirable and anticipated.

4.7 Effects on ability to drive and use machines
Addaven has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
There have been no clinical trials of Addaven.
As a component of the parenteral nutrition administered, it would be extremely difficult to identify adverse reactions that could be attributed directly to Addaven.

Addaven is a reformulation of the product Addamel N, which has been approved in Europe for decades. MRI changes and neurological symptoms have been reported with manganese intake similar to or less than provided with Addamel N. The dose in Addaven has been reduced to a level where these AEs have not been shown to occur.

A minimum infusion time of 8 hours will minimise the risk of oxalosis associated with the infusion of xylitol (see *Section 4.2 Dose and Method of Administration*).

Post- Marketing

For Addamel N and Addaven, the following very rare Adverse Reactions (<1/10000) have been reported in more than 3 patients between October 1982 and September 2015:

System Organ Class	**Frequency**	**Undesirable Effects**
Gastrointestinal disorders:	not known (1)	Nausea, vomiting
General disorders and administration site conditions:	not known (1)	Chills, pyrexia
Nervous system disorders:	not known (1)	Headache

(1) Frequency cannot be estimated from the available data

4.9 Overdose

In patients with impaired renal or biliary function, there is an increased risk of accumulation of trace elements.

Symptoms of zinc poisoning include hypotension, pulmonary oedema, diarrhoea, vomiting, jaundice and oliguria

In case of a chronic overload of iron there is a risk of haemosiderosis, which in severe and rare cases can be treated by venesection.

Refer to *Section 4.2 Dose and Method of Administration* for correct usage.

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Electrolytes in combination with other drugs, ATC code: B05X A31.

Addaven is a mixture of essential trace elements in amounts intended to maintain or help replete the nutritional status, thus preventing or treat the effects of deficiencies of the elements.

5.2 Pharmacokinetic properties

Absorption

For intravenous infusions, absorption of this nutrition is not a pharmacokinetic factor.

Distribution and Metabolism

Individual trace elements will be taken up by tissues to different extents, depending on the requirements within each tissue to maintain or restore the concentration of each element for the metabolic requirements of that tissue.

Excretion
Copper and manganese are normally excreted via the bile, whereas selenium, zinc and chromium (especially in patients receiving intravenous nutrition) are mainly excreted via the urine.
The main route of molybdenum excretion is the urine, although small amounts are excreted in the bile. Iron is eliminated in small amounts by superficial loss and desquamation of gut cells. Premenopausal women can lose 30-150 mg of iron in the monthly blood loss.

5.3 Preclinical safety data
There is no preclinical data of relevance to the safety evaluation beyond those already included in the Data sheet.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Xylitol
Hydrochloric acid (for pH adjustment)
Water for Injections

6.2 Incompatibilites
Addaven may only be added to medicinal or nutritional solutions for which compatibility has been documented. For compatibility information, please refer to section 4.2 Dose and method of administration.

6.3 Shelf-life
Shelf life of the medicine as packed for sale
36 months

Shelf life after mixing with additives
Chemical and physical in-use stability after dilution has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
10 mL polypropylene ampoule
Cartons: 20 x 10 mL polypropylene ampoules

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE
General Sale Medicine

8. SPONSOR
Fresenius Kabi New Zealand Limited
60 Pavilion Drive
Mangere, Auckland 2022
New Zealand
Freecall: 0800 144 892

9. DATE OF FIRST APPROVAL
17 October 1991

10. DATE OF REVISION OF THE TEXT
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