

PRODUCT INFORMATION

Addaven[®]

NAME OF MEDICINE

Addaven is a concentrated trace element solution containing the following simple salts: chromic chloride hexahydrate (CAS No.:10060-12-5), cupric chloride dihydrate (CAS No.:10125-13-0), ferric chloride hexahydrate (CAS No.:10025-77-1), manganese chloride tetrahydrate (CAS No.:13446-34-9), potassium iodide (CAS No.:7681-11-0), sodium fluoride (CAS No.:7681-49-4), sodium molybdate dihydrate (CAS No.:10102-40-6), sodium selenite (CAS No.:10102-18-8) and zinc chloride (CAS No.:7646-85-7).

DESCRIPTION

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

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)

Excipients per 10 mL of Addaven:

Xylitol	3.0 g
Hydrochloric acid	pH adjustment
Water for Injections	qs to 10 mL

Osmolality:	3100 mOsm/kg water
pH:	2.5
Sodium content:	52 µmol (1.20 mg)
Potassium content:	1 µmol (39 µg)

PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

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.

INDICATIONS

To meet basal to moderately increased requirements of trace elements in parenteral nutrition in adults, when either oral or enteral nutrition is inappropriate

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Conditions with total biliary obstruction.
- Wilson's disease, hemochromatosis.
- Children less than 12 years of age

PRECAUTIONS

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 PN 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.

Effects on fertility

The potential effects of Addaven on fertility and general reproductive performance have not been determined.

Use in pregnancy

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

Use in lactation

The active substances in Addaven are excreted in human milk and effects have been shown in breastfed newborns/infants of treated women. Although there is a theoretical risk of zinc-induced copper deficiency in the infant at high Addaven doses, the amount of zinc in the milk may not be sufficient to induce copper deficiency in infants, especially as Addaven also contains copper. The prescriber should consider the benefit/risk relationship before administering Addaven to breastfeeding women.

Paediatric use

Addaven is not recommended for use in children under 12 years of age.

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.

INTERACTIONS WITH OTHER MEDICINES

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 PN mixture may occur, resulting in oxidative loss of ascorbic acid, which can be limited by use of oxygen impermeable bags.

ADVERSE 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 'Dosage and Administration' below).

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

DOSAGE AND ADMINISTRATION

Dosage

The recommended daily dosage of Addaven in patients over 12 years of age 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.

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 PN is 8 hours.

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

Compatibility

Addaven may only be added to medicinal or nutritional solutions for which compatibility has been documented. Compatibility with different products and the storage time of the different admixtures is available upon request.

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.

OVERDOSAGE

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 DOSAGE AND ADMINISTRATION section for correct usage.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or 0800 764 766 (New Zealand)

PRESENTATION AND STORAGE CONDITIONS

Addaven is a concentrated solution for injection which is clear and colourless to slightly yellow.

10 mL polypropylene ampoule

Cartons: 20 x 10 mL polypropylene ampoules

AUST R 244493

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mount Kuring-gai NSW 2080
Australia
Telephone: 1300 361 004

Fresenius Kabi New Zealand Limited
60 Pavilion Drive
Airport Oaks, Auckland 2022
New Zealand
Freecall: 0800 144 892

POISON SCHEDULE OF THE MEDICINE

Australia: Not Scheduled
New Zealand: General Sale Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

29th July 2016