AUSTRALIAN PRODUCT INFORMATION - ADDAVEN® (CHROMIUM, COPPER, IRON, MANGANESE, IODINE, FLUORIDE, MOLYBDENUM, SELENIUM, ZINC)

1 NAME OF MEDICINE

Chromic chloride hexahydrate
Cupric chloride dihydrate
Ferric chloride hexahydrate
Manganese chloride tetrahydrate
Potassium iodide
Sodium fluoride
Sodium molybdate dihydrate
Sodium selenite
Zinc chloride

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)

Excipients with known effect: Xylitol

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Addaven is a concentrated trace element solution for intravenous 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, when either oral or enteral nutrition is inappropriate.

4.2 Dose and method of 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 must be diluted in a compatible parenteral nutrition solution/emulsion or an aqueous diluent before being given as an intravenous infusion, as stated in the "Compatibility' section below.

Additive to a PN solution/emulsion

The recommended infusion time when Addaven is administered as part of Total Parenteral Nutrition (TPN) is 8 to 24 hours in line with the infusion rate of the TPN bag.

Additive to an Aqueous Diluent separate to TPN

When Addaven is used as an additive to an aqueous diluent separate to a TPN bag, one ampoule (10 mL) can be infused over a minimum of 1-hour. The minimum infusion time of 1-hour is based on the safety concerns with xylitol infusion.

Route of Administration

Intravenous, infusion into a central vein.
Peripheral infusion of Addaven may result in local intolerability due to low pH.

It is recommended that a minimum of 1:6 dilution ratio in a compatible aqueous diluent be used for a fast 1-hour infusion rate. The recommendation of the minimum volume of diluent of 50 mL to 10 mL of Addaven can be applied to both fast and slow infusion times. The choice of slow vs. fast infusion times needs to be determined by the Healthcare Professional and will depend on the rate of fluid delivery the patient can receive based on their overall clinical status including renal function, hepatic function and fluid balance.

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 12 years of age

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 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 B_6 deficiency can increase the production of oxalate from xylitol. Adequate levels of vitamin B_6 should be maintained.

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.

Paediatric use

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

Effects on laboratory tests

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

4.5 Interaction with other medicines and other forms of interactions

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

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.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (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.

One ampoule (10 mL) infused over at least 1-hour 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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

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.

See section 4.2 Dose and Method of Administration for correct usage.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

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.

Mechanism of action

No data available.

Clinical trials

No data available.

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Approved Shelf Life as packaged 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
AUST R 244493

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure
Chemical structures of the active ingredients are not provided as these are simple salts.

CAS number

Active Substance	CAS number
Chromic chloride hexahydrate	10060-12-5
Cupric chloride dihydrate	10125-13-0
Ferric chloride hexahydrate	10025-77-1
Manganese chloride tetrahydrate	13446-34-9
Potassium iodide	7681-11-0
Sodium fluoride	7681-49-4
Sodium molybdate dihydrate	10102-40-6
Sodium selenite	10102-18-8
Zinc chloride	7646-85-7

7 MEDICINE SCHEDULE (POISONS STANDARD)
Australia: Not Scheduled

8 SPONSOR
Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mount Kuring-gai, NSW 2080
Australia
Telephone: (02) 9391 5555

9 DATE OF FIRST APPROVAL
29 July 2016

10 DATE OF REVISION
09 January 2024

Summary table of changes

Section Changed	Summary of new information
4.2	Method of administration changed *to* include dosing instructions. Dilution ratios added, and clarification on diluents to be used and safety statements on xylitol and fast vs. slow infusion added.
4.8	Adverse effects section changed to state that 'One ampoule (10 mL) infused over at least 1-hour will minimise the risk of oxalosis associated with the infusion of xylitol'.