Australian Government
Department of Health
Therapeutic Goods Administration

# AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for nine trace elements including chromic chloride

Proprietary Product Name: Addaven

Sponsor: Fresenius Kabi Australia Pty Ltd

**Date of CER: September 2015**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

# About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

# Contents

# List of common abbreviations

| Abbreviation | Meaning |
|---|---|
| ACPM | Advisory Committee on Prescription Medicines |
| ACSOM | Advisory Committee on the Safety of Medicines |
| ADEC | Australian Drug Evaluation Committee |
| ADI | Acceptable Daily Intake |
| AE | adverse event |
| ARTG | Australian Register of Therapeutic Goods |
| ASA | Australian Specific Annex |
| ASPEN | American Society for Parenteral and Enteral Nutrition |
| AUC | area under the plasma drug concentration-time curve |
| $AUC_{t1-t2}$ | area under the plasma drug concentration-time curve from t1 to t2 |
| AuSPEN | AustralAsian Society for Parenteral and Enteral Nutrition |
| Cmax | maximum serum concentration of drug |
| CMI | Consumer Medicine Information |
| Cr | chromium |
| Cu | copper |
| ESPEN | European Society for Clinical Nutrition and Metabolism |
| F | fluorine |
| FDA | Food and Drug Administration (US) |
| Fe | iron |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| I | iodine |
| IV | intravenous |
| Mn | manganese |

| Abbreviation | Meaning |
|---|---|
| Mo | molybdenum |
| PD | pharmacodynamic(s) |
| PI | Product Information |
| PK | pharmacokinetic(s) |
| PN | Parenteral Nutrition |
| PO | per os (oral administration) |
| RMP | Risk Management Plan |
| SAE | serious adverse event |
| Se | selenium |
| t½ | elimination half life |
| TE | trace elements |
| Tmax | Time taken to reach the maximum concentration (Cmax) |
| TPN | Total Parenteral Nutrition |
| Zn | zinc |

# 1. Introduction

This is a literature based submission (LBS) to register a new chemical entity.

## 1.1. Drug class and therapeutic indication

Addaven is a product for single-use only and contains nine trace elements as the active ingredients, which are all considered to be simple inorganic salts.

The proposed indication is:

> *To meet basal to moderately increased requirements of trace elements in parenteral nutrition.*

## 1.2. Dosage forms and strengths

The submission proposes registration of the following dosage forms and strengths:

Addaven 10 mL polypropylene ampoules containing:

- Chromic chloride 53.3mcg
- Cupric chloride dehydrate 1.02mcg

- Ferric chloride hexahydrate 5.40mcg
- Manganese chloride 198mcg
- Potassium iodide 166 mcg
- Sodium fluoride 2.10mcg
- Sodium molybdate dehydrate 48.5mcg
- Sodium selenite 173mcg
- Zinc chloride 10.5mcg

## 1.3. Dosage and administration

### 1.3.1. Dosage

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.

### 1.3.2. Method of administration

Addaven must not be given undiluted. Addaven shall be given as an intravenous infusion, diluted in a parenteral nutrition solution/emulsion.

A 10mL ampoule of Addaven can be added to the following intravenous solutions:

**Table 1: Addaven IV solutions.**

| Admixture | Volume |
|---|---|
| Glucose 5% | 100 – 1000 mL |
| Glucose 10% | 100 – 500 mL |
| Sodium Chloride 0.9% | 50 – 500 mL |

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

### 1.3.3. 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.

### 1.3.4. 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.

# 2. Clinical rationale

Addaven is a fixed combination of TE in amounts normally absorbed from the oral diet. Patients receiving PN without adequate TE provision have shown deficiency of several TE. The 10 TE

which are considered essential in humans are chromium, cobalt, copper, fluoride, iodide, iron, manganese, molybdenum, selenium, and zinc.

# 3. Contents of the clinical dossier

The submission contained the following clinical information:

- Multiple literature references and guidelines
- other efficacy/safety studies - supporting a 9 trace elements supplement (Addamel N)
- PSURs

# 4. Pharmacokinetics

## 4.1. Studies providing pharmacokinetic data

The product was designed to have no pharmacodynamic effects besides maintaining or repleting the nutritional status of the contained trace elements.

No data has been published about the pharmacokinetics of trace elements when provided intravenously.

Those trace elements which are primarily excreted in the urine are chromium, molybdenum, selenium, iodine, and fluoride while trace elements for which the main route of excretion is via the bile are copper and manganese.[1] Excretion of zinc is mainly in the faeces by transport through the intestinal mucosa, with a smaller amount in the bile and in urine.[2] Infusion with zinc enhances distal renal reabsorption of zinc but infusion with amino acids increases proximal zinc secretion in the kidney that may result in increased urinary losses of zinc. However, amino acid loss in urine is usually small. Iron losses are by way of desquamated skin, normal turnover of gut cells, and blood loss; hence is not under direct control.

Thus caution is required in patients with severe renal or hepatic dysfunction.

## 4.2. Physicochemical characteristics of the active substance

The following information is derived from the Sponsor's summaries.

Allwood and co-workers showed that iron and copper might interact to form microscopic precipitates by reaction with components of the PN regimen (Allwood and Greenwood 1992; Allwood and Kearney 1998). Harmful effects were not related to them and this did not cause any measurable loss of TE. The formation of copper and iron precipitates and the factors influencing their formation in PN mixtures containing Additrace and 1 of the commercial amino acids solutions Vamin or Synthamin has been studied (Allwood et al 1998). The authors concluded that iron and copper can contribute to precipitation in stored PN mixtures. Among other factors, the amount of precipitates depended on the type of amino acid solution, the permeability of the bag for hydrogen sulphide, and the concentration of copper. The concentration of copper in Addamel N of 1.26 mg (20.0 µmol) per 10 mL has been reduced to 0.38 mg (6.0 µmol in Addaven). The amounts of both iron and copper in Addaven are small; hence, the potential for precipitates is low. To avoid incompatibilities with other IVN

[1] Food and Nutrition Board 2001; Food and Nutrition Board 2000; Food and Nutrition Board 1997
[2] Jeejeebhoy 2009

components, Addaven must only be mixed with other medicinal products for which compatibility has been documented.

Molybdenum interacts with copper to form complexes that increase urinary elimination of copper. This interaction may lead to copper deficiency and is used to promote copper excretion in patients with Wilson's disease (Johnson 1997).

Amino acids, which are present in all total IVN mixtures, could complex with zinc and copper and the complex could be excreted in urine (Berthon et al 1980). However, amino acid loss in urine is usually small. Renal TE loss occurs only in significant amounts if amino sugars are present. In the past, amino sugars might have resulted from the Maillard reaction in the presence of glucose during sterilization in the process of the amino acid production (Stegink et al 1981). Nowadays, amino sugars are rarely present in amino acid preparations because the amino acids are sterilized separately from glucose.

Potential interactions between calcium and phosphate give rise to concerns about more substantial precipitates and serious side effects (National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition 1998). In the early days of parenteral nutrition, the group of Burnham studied intravenous feeding mixtures containing fat emulsion and TE of the Addamel product line, and concluded that the only concern was possible droplet coalescence at high concentrations of calcium and magnesium (Burnham et al 1982; Burnham et al 1982). Addaven contains no calcium, magnesium or phosphate.

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 (Allwood and Kearney 1998). Selenious acid or selenite ions were suggested to be reduced by ascorbic acid to selenium that is not bioavailable. However, in vitro studies demonstrated that this reaction only occurred in more acidic solutions than those found in IVN bags (Ganther and Kraus 1989). This is confirmed by the beneficial effects of sodium selenite in PN regimens (Malone et al 1989; Lane et al 1987; Mansell 1989).

Gibbons and co-workers (Gibbons et al 2001) studied the effect of temperature and TE on the anaerobic degradation of dehydroascorbic acid in a standard PN mixture of 15 amino acids (Synthamin 14, Baxter), glucose 20%, and Addamel N. Inclusion of TE had no effect on the rate of degradation of dehydroascorbic acid, the degradation product of ascorbic acid. Ascorbic acid is known to be oxidised by dissolved oxygen to dehydroascorbic acid, catalysed by TE in the PN solution (in particular copper). Dehydroascorbic acid is an active substance with beneficial effects on various tissues.

### 4.3. Evaluator's overall conclusions on pharmacokinetics

There is no PK data to evaluate, essentiality and dosing is based on deficiency states and guidelines, which are reasonably well established. The only essential trace element missing is cobalt - only known requirement for cobalt is within the functional group of the haematopoietic factor vitamin B12, routinely provided as part of the vitamin supply to patients receiving PN.

## 5. Pharmacodynamics

To avoid repetition and provide continuity of content these are evaluated under "Efficacy".

## 6. Dosage selection for the pivotal studies

Not applicable.

# 7. Clinical efficacy

PDs are also evaluated here under Efficacy to avoid repetition and provide continuity of content.

**Table 2: TE composition of in a daily dose of 10mL Addaven.**

| Trace element | Source | Daily dose | |
|---|---|---|---|
| | | mcmol | mg |
| $Cr^{3+}$ | chromic chloride | 0.2 | 0.01 |
| $Cu^{2+}$ | cupric chloride dehydrate | 6.0 | 0.38 |
| $Fe^{3+}$ | ferric chloride hexahydrate | 20 | 1.10 |
| $Mn^{2+}$ | manganese chloride | 1 | 0.055 |
| $I^-$ | potassium iodide | 1 | 0.13 |
| $F^-$ | sodium fluoride | 50 | 0.95 |
| $MoO_4^{2-}$ (as $Mo^{6+}$) | sodium molybdate dehydrate | 0.2 | 0.019 |
| $SeO_3^{2-}$ (as $Se^{4+}$) | sodium selenite | 1 | 0.08 |
| $Zn^{2+}$ | zinc chloride | 77 | 5.0 |

No clinical studies with Addaven have been performed. Five clinical trials were performed for the initial registration of Addamel N in Europe.

## 7.1. Efficacy of respective trace elements

### 7.1.1. Chromium

There is a registered IV product containing chromic chloride 0.11mg/5mL, the proposed dosage is 0.01mg/10mL chromium as the trivalent Cr.

The absorbed amount of chromium from a standard adult oral diet is only 0.4–0.9 mcg/d. Based on oral absorption in healthy individuals, the parenteral requirements may be as low as 0.14–0.87 mcg/d.[3]

The main effects of deficiency are reduced insulin activity resulting in impaired glucose tolerance, increased free fatty acids in plasma, and weight loss. Serum Chromium levels may not reflect the level of cellular deficiency. Treatment with chromium alleviates the impaired GTT (at higher doses Anderson et al 1997). A meta-analysis of studies involving diabetic subjects revealed that "A study of 155 diabetic subjects showed that chromium reduced glucose and insulin concentrations; the combined data from the other studies did not" (Althuis et al. 2002). In all these studies ≤ 200mcg Cr was administered daily. However, a recent double-blind crossover study in India of subjects with type 2 diabetes indicated that Cr supplementation (400mcg Cr/d) for 12 weeks lowered serum insulin and glucose levels (Ghosh et al. 2002).

Cr is used in the formation of chromodulin (originally termed low-molecular-weight Cr-binding substance) which may be involved in lipid metabolism.

> *Comment: Much of this is from Recent advances in the nutritional biochemistry of trivalent chromium J. B. Vincent Proceedings of the Nutrition Society (2004). 63. 41.*

His conclusion states:

The daily requirement for human subjects is small, i.e. approximately 30mcg, such that it is difficult for healthy individuals to develop Cr deficiency. Thus, the use of Cr supplements is probably unnecessary for the general public. However, the use of certain Cr supplements, such as Cr(pic)3, (Chromium picolinate) is probably harmful.

[3] A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi–Trace Element Products Nutrition in Clinical Practice Volume 27 Number 4 August 2012 440-491.

- S. Jacobson and P.-O. Wester (1977). Balance study of twenty trace elements during total parenteral nutrition in man.[4] From 4 male patients over 5 days they recommended 0.05mg/day.
- Phillips & Garnys. (1981) Trace Element Balance in Adults Receiving Parenteral Nutrition: Preliminary Data[5] looked at 3 patients. Cr and Se were not given, except as contaminants, and there were negative balances of these elements in all 3 patients. They found In order to avoid the problems of fixed formulae trace element mixtures, it would be more reasonable to use single solutions, as recommended by an Expert Panel.
- Phillips & Garnys. (1981) Parenteral Administration of Trace Elements to Critically III Patients[6] in balance studies on 8 patients found for chromium an input of up to 100mcg/day resulted in zero or negative balances in all patients.

Some studies found that over time serum chromium rose when added to the infusion.

- Btaiche et al (2011) Dosing and Monitoring of Trace Elements in Long-Term Home PN[7] A retrospective analysis of results. The mean daily chromium dose to 26 patients was 9.33 ± 0.42mcg.

Eight patients had chromium supplementation withheld in their PN in response to elevated serum chromium concentrations. "Although trace elements supplements are relatively safe, identifying the exact trace elements requirements in PN is challenged by the poor correlation of serum trace elements concentrations with tissue trace elements stores and the presence of underlying clinical conditions that variably affect trace elements balance."

- Howard et al (2007) Autopsy Tissue Trace Elements in 8 Long-Term Parenteral Nutrition Patients Who Received the Current U.S. Food and Drug Administration Formulation[8] While measuring plasma or serum trace element levels may indicate deficiency or excess in patients not receiving a trace element infusion, balance studies have shown that plasma or serum values are not reliable indicators of body stores or nutrient adequacy in patients receiving daily trace element infusions. Chromium had a 10- to 100-fold higher than normal concentrations in nearly all tissues studied.

Deficiency on TPN

- Jeejeebhoy et al (1977) Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition[9] who responded to chromium found that it "suggests that it is an essential trace element in human nutrition and should be included in any regimen for TPN. The optimum amounts are as yet undetermined but preliminary studies in this patient suggest that it may approximate 20mcg/day."

### 7.1.2. Copper

There is a registered IV product containing cupric chloride dihydrate 2.8mg/5mL, the proposed dose is 0.38mg/10mL.

The recommended dose of copper in adult parenteral multiple trace elements products should be lowered to 0.3–0.5mg/d.[10]

[4] British Journal of Nutrition,37, pp 107-126.
[5] Journal of Parenteral and Enteral Nutrition Jan 1, 1981 vol 5 no. 1 page 11.
[6] Anaesth Intens Care (1981). 9. 221.
[7] Journal of Parenteral and Enteral Nutrition / Vol. 35, No. 6, November 2011.
[8] Journal of Parenteral and Enteral Nutrition September–October 2007 Vol. 31, No. 5 page 388.
[9] The American Journal of Clinical Nutrition 30: April 1977. pp. 53 1- 538.
[10] A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi–Trace Element Products.

Copper metalloenzymes act as oxidases and reduce molecular oxygen, they include amine oxidases (important in histamine and serotonin metabolism), lysyl oxidase (needed for cross-linking of elastin and collagen), ferroxidase (important in iron metabolism), and cytoplasmic superoxide dismutase (a part of the antioxidant defences of the body. The clinical effects of deficiency are therefore largely a result of the impaired iron metabolism, leading to anaemia, and impaired elastin and collagen function.

It is likely that copper accumulates as a result of liver disease but it is also possible that hepatic copper overload enhances the liver damage.

- Jacobson and Wester (1977) Balance study of twenty trace elements during total parenteral nutrition in man recommended 0.1mg/day[11] for a 70 kg man.
- Phillips & Garnys. (1981) Parenteral Administration of Trace Elements to Critically III Patients[12] found "0.3-0.8 mg/ day resulted in positive balances in all but two patients, suggesting that the lower limit of the AMA recommended doses (0.5mg/day) is a reasonable figure. Serum copper levels increased in all but one patient."
- Shike et al (1981) Copper Metabolism and Requirements in Total Parenteral Nutrition[13] found "The amount of copper required to achieve balance in adult patients maintained on TPN amounts to 0.30 mg/ day. In the presence of diarrhoea or excessive fluid losses through gastrointestinal stomas or fistulas, this amount has to be increased to 0.40-0.50 mg/day. In patients with abnormalities of the liver excretory system, the amount of infused copper has to be decreased by about 0.15 mg/ day." And "The presence of trace elements as contaminants in the TPN solutions constitutes a problem."
- Shenkin et al (1987) Maintenance of Vitamin and Trace Element Status in Intravenous Nutrition using a Complete Nutritive Mixture[14] serum copper rose progressively over up to 25 days of Adamel N.
- Btaiche et al (2011) Dosing and Monitoring of Trace Elements in Long-Term Home Parenteral Nutrition Patients[15] had a mean daily copper dose 0.99 ± 0.03mg. The mean serum copper concentration was 1.25 ± 0.20mcg/mL. Of 40 serum copper concentrations measured, 31 (77.5%) were within and 9 (22.5%) above the reference range. "Study results show that the average daily copper dose far exceeded A.S.P.E.N.'s guidelines, and most (95.5%) of the doses were above the recommended dosing range. Serum copper concentrations were maintained within the normal range in 77.5% of cases, with the remaining serum concentrations above normal levels."
- Davis et al (1987) Plasma Vitamin and Mineral Status in Home Parenteral Nutrition Patients[16] used 1mg/day: "Patient values were at the upward end of the normal range, and frequently exceeded this range. Mean patient values ranged from 1.35 ± 0.25mcg/mL in September to 1.79 ± 0.33mcg/mL in April."

There were multiple other reports of Cu being added to TPN.

- Howard et al (2007) Autopsy Tissue Trace Elements in 8 Long-Term Parenteral Nutrition Patients Who Received the Current U.S. Food and Drug Administration Formulation.[17] With 1.4mg of copper added/day to 8 patients whose average duration on HPN was 14 years (range, 2–21 years) "Copper was present at normal concentrations in heart and skeletal

[11] Table 6 page 123 of article
[12] Anaesth Intens Care (1981). 9. 221
[13] Gastroenterology 1981:81:200-7
[14] Journal of parenteral and enteral nutrition 1987: 11; 5 p 238
[15] Journal of Parenteral and Enteral Nutrition Vol. 35, No. 6, November 2011 page 736
[16] Journal of Parenteral and Enteral Nutrition Vol. 11 . No.5 1987 Page 480
[17] Journal of Parenteral and Enteral Nutrition Vol. 31, No. 5 page 392

muscle in all patients but very elevated in liver and kidney, especially in those who died in liver failure."

Deficiency on TPN

- There are multiple case reports of deficiency on copper free TPN with resulting symptom response to copper.
- The main signs and symptoms of copper deficiency reported in adults have been hypochromic anaemia, neutropenia or pancytopenia. One case showed the reversibility of the symptoms when copper was removed from the intravenous regimen and subsequently reintroduced (Fuhrman et al 2000[18]).

### 7.1.3. Fluoride

There is no registered IV product containing fluoride, proposed dosage is 0.95mg/10mL.

> *The evidence for fluoride requirement during PN is sparse.*
>
> *This level (1mg/day) of intravenous intake has therefore been used for nearly 40 years in Europe with no reports of any safety issues.*

With a proposed daily dose of 10mL the daily dose of sodium fluoride provides 0.95mg fluoride[19] as $F^-$.

The reference provided in relation to fluoride requirements has these comments:

> *Body fluid and tissue fluoride concentrations are proportional to the long-term level of intake; they are not homeostatically regulated.*
>
> *Fluoride in bone appears to exist in both a rapidly exchangeable pool and a slowly exchangeable pool.*
>
> *At this time, therefore: the use of balance data to estimate an adequate Intake of fluoride is not warranted*
>
> *Because data are not available to determine an Estimated Average Requirement (EAR), the reference value that will be used for fluoride is the Adequate Intake (AI). The AI is based on estimated intakes that have been shown to reduce the occurrence of dental caries maximally in a population without causing unwanted side effects including moderate dental fluorosis.*
>
> *AI for Males ≥ 19 years and over 4mg/day.*
>
> *AI for Females ≥ 19 years and Pregnancy 3mg/day.*
>
> *The risk of developing early signs of skeletal fluorosis is associated with a fluoride intake greater than 10mg/day for 10 or more years. Therefore, a Tolerable Upper Intake Level (UL) of 10mg/day was established for children older than 8 years and for adults.*
>
> *In the absence of high dietary concentrations of calcium and certain other cations with which fluoride may form insoluble and poorly absorbed compounds, 80 percent or more is typically absorbed.*

The following is from the Clinical Overview:

> *As well as the dental effect fluoride also has the unique ability to stimulate new bone formation. In bone it appears to exist in both a rapidly exchangeable pool and a slowly exchangeable pool. The former is located in the hydration shells on bone crystallites, where fluoride may be exchanged iso-ionically or hetero-ionically with ions in the surrounding*

[18] Journal of Parenteral and Enteral Nutrition 2000 24:No.6 page 361
[19] 2.6.1 Non-Clinical Summary: Introduction (Trace Elements) page 3

> *extracellular fluids. Mobilization from the slowly exchangeable pool results from the resorption associated with the process of bone remodelling.*

Another reference (the A.S.P.E.N. Position Paper[20]) states:

> *Supplementation of PN with fluoride could be beneficial, but more research is needed for adult, paediatric, and neonatal patient populations.*

Even allowing for a reduction in the amount absorbed the proposed daily dose of 0.95 mg is considerably less than the Adequate Intake of 3 & 4mg/day.

### 7.1.4. Iodine

There is no registered IV product containing iodine, proposed dosage is 0.13mg/10mL.

With a proposed daily dose of 10mL the daily dose of potassium iodide provides 0.13mg iodine[21] as $I^-$. From the reference provided[22] the Recommended Dietary Allowance is 0.15mg/day of iodine.

Iodine is an essential component of the thyroid hormones, i.e. thyroxine and triiodothyronine. These hormones and, therefore, iodine are essential for life.

Another reference (the A.S.P.E.N. Position Paper[23]) states:

> *Since skin cleansing has widely moved to the use of 2% chlorhexidine, the risk of iodide deficiency and the need for parenteral supplementation need to be investigated. Routine supplementation of PN with iodide could be beneficial, but more research is needed for adult, paediatric, and neonatal products.*

- Zimmermann (2009) Iodine: It's Important in Patients that Require Parenteral Nutrition[24] 'Daily iodine requirements in adults receiving enteral nutrition or PN are estimated to be 70–150g, but most PN formulations do not contain iodine. Despite this, deficiency is unlikely because absorption from iodine-containing skin disinfectants and other adventitious sources can provide sufficient iodine. However, if chlorhexidine replaces iodine-containing disinfectants for catheter care, iodine deficiency may occur during long-term PN, and periodic testing of thyroid functions may be prudent.'

  > *Iodine deficiency symptoms have not been reported with in-hospital intravenous nutrition support.*

- Ishizuka et al (2011) Sequential Evaluations of Trace Elements in Patients Receiving Parenteral Nutrition[25] using 0.13mg/day showed essentially no change in total and free $T_3$ and $T_4$.

### 7.1.5. Iron

There is no registered IV product containing ferric chloride hexahydrate, with a proposed daily dose of 10mL the daily dose of ferric chloride hexahydrate provides 1.10mg iron[26] as $Fe^{3+}$. This dose (1.1mg or 20mcmol) in Addaven is the amount recommended by both ESPEN and AuSPEN.

From the reference provided[27] adult men need to absorb only about 1mg/day to maintain iron balance. The average requirement for menstruating women is somewhat higher, approximately

[20] A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi–Trace Element Products
[21] 2.6.1 Non-Clinical Summary: Introduction (Trace Elements) page 3
[22] Food and Nutrition Board 2001
[23] A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi–Trace Element Products
[24] Gastroenterology 2009;137:S36–S46
[25] Hepato Gastroenterology 58 (2011) 1466
[26] 2.6.1 Non-Clinical Summary: Introduction (Trace Elements) page 3

1.5mg/ day. There is, however, a marked interindividual variation in menstrual losses, and a small proportion of women must absorb as much as 3.4mg/day. Towards the end of pregnancy, the absorption of 4 to 5mg/day is necessary to preserve iron balance.

About two-thirds of the body iron is found in haemoglobin in erythrocytes. The remainder is in myoglobin and enzymes that are primarily necessary for oxidative metabolism. The body normally has stores of iron in the liver and bone marrow. Deficiency of iron leads to anaemia.

- Kumpf (2003) Update on Parenteral Iron Therapy[28] Because most patients who need PN receive it on a short-term basis (e.g. < 3 months), iron stores are usually adequate to meet daily iron requirements. Rather than waiting for iron deficiency anaemia to develop in a long-term PN patient before initiating parenteral iron, some clinicians prefer providing maintenance therapy. However, this practice is controversial and not well supported.

The routine supplementation of iron in these patients may expose them to the unnecessary risk of adverse reactions and result in iron overload, so it is therefore not recommended.

Conflicting data exist regarding the association between iron therapy and infection. Theoretically it appears to relate to saturation of transferrin with resultant free iron levels.

#### *7.1.5.1. Iron deficiency*

In relation to deficiency Forbes & Forbes (1991)[29] reported iron deficiency, resulting in a microcytic anaemia in 14/49 patients 0-8 y (mean 25 months) after starting TPN. However 2 patients had deficiency at the start of treatment and in 6 patients, additional factors were likely to have contributed leaving 6/49 (12%). Similarly while Khaodhiar et al (2002)[30] reported 30 of 55 patients on TPN for ≥ 6 months had iron deficiency 10 patients had it at the start of treatment; 13 had episodes of acute blood loss that caused acute iron-deficiency anaemia. Leaving 7/55 patients (13%). However, the authors contended that most patients (24), including those with episodes of acute blood loss, slowly progressive iron deficiency also developed during subsequent periods without evidence of acute blood loss.

### 7.1.6. Manganese

There is a registered IV product containing manganese chloride 3.7mg/5mL, the proposed dosage is 0.055mg/10mL.

One of the references provided (Leach and Harris 1997) states:

> *balance studies which have provided estimates in the range of 0.05-3.5mg/day.*

Another reference (the A.S.P.E.N. Position Paper[31]) states:

> *A.S.P.E.N. recommends that the dose of manganese in parenteral multiple trace elements products be decreased to 55mcg/d for adults.*

Manganese is involved in the activity of many metalloenzymes, including arginase, glutamine synthetase, and manganese superoxide dismutase, and also in the activity of glycosyl transferases (though evidence is lacking in man). From the blood stream, it is taken up from the liver and bound to transferrin and albumin for distribution to tissues.

There have been conflicting results on the dosing for TPN:

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[27] Food and Nutrition Board 2001
[28] Nutrition in Clinical Practice 18:318–326, August 2003
[29] Micronutrient Status in Patients Receiving Home Parenteral Nutrition *Nutrition* vol 13, Nos. 11/12,1991.941
[30] Iron Deficiency Anaemia in Patients Receiving Home Total Parenteral Nutrition Journal of Parenteral and Enteral Nutrition Vol. 26, No. 2. 2002
[31] A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi–Trace Element Products

- Phillips and Garnys (1981b) showed 0.1-0.3mg/day maintained balance.
- Papageorgiou et al (2002) showed a decrease in serum manganese after a mean 20 days of 0.3mg/day.
- Falbe et al (1987) showed a decrease in serum manganese after 7 days of 0.3mg/day while 0.6mg/day maintained it.
- Tulikoura and Vuori (1986) in malnourished (lost 10% or more of their body weight or if serum protein was below 56g/L) preoperative patients showed 2.5mg/day over 10-12 days, maintained, but did not elevate, the manganese concentration in muscle and liver.
- Howard et al (2007) showed that 0.7mg/day led to an increase in tissue concentrations in liver, but not in muscle, heart or kidneys, at autopsy.
- Takagi et al (2002) found whole blood manganese increased markedly on 1.1mg/day and slightly with 0.11mg/day, but did not increase with 0.055mg/day.
- Ishizuka et al (2011) showed that an intake of 0.055mg/day) led to no change to serum levels in patients on TPN over about 1 month.

#### *7.1.6.1. Manganese overload*

There have been a number of reports of patients receiving long-term PN (with intakes ranging from 2-40mcmol/day [0.110-2.20mg/day]), who appeared to have accumulated manganese in the basal ganglia of the brain.

Abnormal midbrain MRI images, some memory loss with muscle weakness, signs suggestive of Parkinsonism have occurred. Some of these features have been shown to be reversible on cessation of manganese.

Elevation of serum Manganese has been associated with increased MRI intensity but no clinical signs.

Takagi et al (2002) found whole blood manganese showed good correlation with the changes in MRI, whereas plasma manganese had a poorer correlation.

There is an association of increased serum or whole blood manganese in patients with cholestasis, especially in infants.

#### *7.1.6.2. Manganese deficiency on TPN*

Only 1 case reported (abstract only), in a [information redacted] who had received PN since 9 days after birth. The patient had short stature, abnormal bony metaphysis and diffuse bone demineralization. When manganese was provided catch-up in height occurred, together with bone improvements.

### 7.1.7. Selenium

There is a registered IV product containing sodium selenite decahydrate 111mcg/5mL (24mcg selenium or 0.3mcmoles in 5mLs).

With a proposed daily dose of 10mL the daily dose of sodium selenite provides 0.08mg selenium[32] as $Se^{4+}$. One of the references provided (Shenkin 2009) states:

> *There is substantial individual variation in requirements for Se in health, so supply in PN must at least meet the dietary Reference Nutrient Intake, which as summarized earlier is probably in the range of 55–70g/day.*

[32] 2.6.1 Non-Clinical Summary: Introduction (Trace Elements) page 3

> *Most of the studies to evaluate Se requirements during PN have been in patients receiving long-term PN at home because this is the group in which biochemical and clinical evidence of Se deficiency largely has been observed.*
>
> *Taken overall the following conclusions can be reached.*
>
> *An intake of 30–50g/day meets the ongoing requirements of some patients, probably those with basal requirements, but it is inadequate to correct Se depletion.*
>
> *An intake of 63g/day is adequate for the majority of home patients, but about 15% have a higher requirement than this. An intake of 85g/day seems to be sufficient to maintain tissue concentrations in most patients, although some may have even higher requirements.*

Selenium through its presence in the amino acid selenocysteine is in a number of proteins, i.e. selenoproteins. These include: 4 known glutathione peroxidases that defend against oxidative stress; three iodothyronine deiodinases that are important in thyroid hormone metabolism; and 3 thioredoxin reductases that help to regulate the redox status of vitamin C and other molecules.

Selenium deficiency seldom causes overt illness if it occurs in isolation. It may lead to biochemical changes that predispose to illness if associated with other stresses.

There have been multiple studies of doses of 0.020-0.120mg/day with varying results.

- Btaiche et al (2011) found that in patients on PN for more than 1 year, made, a mean selenium intake of 0.0 69mg/day led to 60 % of serum selenium measurements results being within the reference range, 38 % below it, and 2 % being above it.
- Buchman et al (1994) suggested the variable requirements of individual patients may be due not only to the variable effects of disease, but also to some impairment in renal homeostasis in those on long-term PN.

While 0.03mg/day was adequate to maintain selenium status over standard short PN feeding periods, patients more seriously ill, e.g. severe burns, sepsis, required higher intakes of selenium.

There exists controversy over whether an intake which maximizes plasma glutathione peroxidase activity is necessary, or an intake which maintains two-thirds maximum activity is sufficient. 'However, increased oxidative stress is likely in illness, hence optimizing glutathione peroxidase activity, and other selenoproteins would seem logical.'

#### *7.1.7.1. Selenium deficiency on TPN*

Changes reported include nail and hair changes, skeletal muscle myopathy, reversible cardiomyopathy and fatal cardiomyopathy.

Studies with no added selenium supplement showed that removal of supplements for 4 months led to a significant fall in plasma selenium and in red blood cell glutathione peroxidase.

### 7.1.8. Zinc

There are registered IV products containing zinc chloride 5mg/2mL.

With a recommended daily dose of 10mL the daily dose of zinc chloride provides 5mg zinc[33] as $Zn^{2+}$. One of the references provided (Jeejeebhoy 2009) states:

> *In TPN the requirements have been estimated by balance studies to be 3mg/d in patients without gastrointestinal losses and a mean of 12 mg/d in patients with diarrhoea and fistula losses.*

[33] 2.6.1 Non-Clinical Summary: Introduction (Trace Elements) page 3

Nearly 100 specific enzymes depend on zinc for catalytic activity. These enzymes occur in all enzyme classes and have wide ranging roles throughout metabolism. The roles in RNA polymerase and protein synthesis, alcohol dehydrogenase, carbonic anhydrase, and alkaline phosphatase have been particularly well studied. Moreover, zinc can facilitate protein folding, i.e., forming 'zinc fingers' which hold roles in gene regulation as DNA binding transcription factors.

Wolman et al (1979) found in patients with gastrointestinal disease, an intake of approximately 50mcmol/day (3.2mg/day) maintained zinc balance in the absence of gastrointestinal losses, an intake of about 90mcmol/day (5.9mg/day) almost achieved balance in most other patients, whereas an intake of 180mcmol/day (11.7mg/day) achieved a positive balance in all patients.

A dose of 6.5mg/day was used in Addamel N, although there have been no cases of harm, this amount was felt unnecessary for the majority of patients. It was therefore reduced in Addaven to 5mg (77mcmol)/day.

#### *7.1.8.1. Zinc deficiency on TPN*

A large number of cases have been published. The main features of this are an eczematous rash, involving the face, flexures and perineal region; other features include nail changes, alopecia, mental apathy and depression, visual dysfunction, and impaired immune function. These symptoms reverse readily: usually within a few days of zinc supplementation either or with intravenous zinc, usually about 10mg/day.

- Btaiche et al (2011) found that a mean intake of 9.1mg/day (140mcmol/day) in patients with short bowel syndrome, and of 6.7mg/day (103mcmol/day) in non-short bowel syndrome patients, maintained a normal plasma zinc concentration in more than 90% of patients.

### 7.1.9. Molybdenum

There is no registered IV product containing sodium molybdate dehydrate.

With a recommended daily dose of 10mL the daily dose of sodium molybdate dehydrate provides 0.019mg molybdenum as $Mo^{6+}$.

AusPEN guidelines[34] recommend 0.019mg/ day.

Molybdenum functions as a cofactor for a small number of enzymes in man, i.e., sulphite oxidases, xanthine oxidases, and aldehyde oxidases. Dietary molybdenum deficiency has not been seen in healthy people without a genetic defect that prevents sulphite oxidase synthesis and leads to severe neurological damage.

Another reference (the A.S.P.E.N. Position Paper[35]) states:

> *There are no significant data to warrant recommending routine molybdenum supplementation in PN formulas.*

Phillips and Garnys (1981) showed balances of 0.1-0.2mg/day.

Doses of 0.02mg/day to 0.2mg/day have been reported.

#### *7.1.9.1. Molybdenum deficiency on TPN*

Only 1 case reported in an adult male who had been receiving PN for about 1 year, who then developed progressive tachycardia, tachypnoea, neurological and visual changes, and eventually

[34] Australasian Society for Parenteral and Enteral Nutrition guidelines for supplementation of trace elements during parenteral nutrition Osland et al Asia Pac J Clin Nutr 2014;23(4):545-554
[35] A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi–Trace Element Products

coma. Treatment with ammonium molybdate improved the clinical condition, reversed the sulphur handling abnormality, and normalized uric acid production.

## 7.2. Studies relating to Addamel or Addamel N

As can be seen from the following table there were 4 studies that indicated the constitution of the electrolyte solution used. Only Shenkin et al (1987) and Malone et al (1989) clearly used similar preparations (Addamel N & Additrace). Two other studies only gave the concentrations given of the relevant elements studied, though both indicated Additrace was used.

**Table 3: Daily dose used in studies claimed related to Addaven**

| Trace element | Addaven | Addam Electrolyte[a] | Addamel[b] | Addamel N[c] | Additrace[d] |
|---|---|---|---|---|---|
| | mcmol | mcmol | mcmol | mcmol | mcmol |
| $Cr^{3+}$ | 0.2 | | | 0.2 | 0.2 |
| $Cu^{2+}$ | 6.0 | 5 | 5 | 20 | 20 |
| $Fe^{3+}$ | 20 | 50 | 50 | 20 | 20 |
| $Mn^{2+}$ | 1 | 40 | 40 | 5 | 5 |
| $I^-$ | 1 | 1 | | 1 | 1 |
| $F^-$ | 50 | 50 | | 50 | 50 |
| $MoO_4^{2-}$ (as $Mo^{6+}$) | 0.2 | | | 0.2 | 0.2 |
| $SeO_3^{2-}$ (as $Se^{4+}$) | 1 | | | 0.4 | 0.4 |
| $Zn^{2+}$ | 77 | 20 | 20 | 100 | 100 |
| Calcium | | 5000 | 5000 | | |
| Magnesium | | 1500 | 1.500 | | |

[a] In 5mL not 10mL balance (Jacobson and Wester 1977); [b] (Shenkin et al 1986); [c] (Shenkin et al 1987); [d] (Malone et al 1989).

Reynolds et al (1998) used Additrace but looked only at manganese, while Cruickshank et al (1989) also used Additrace but looked only at copper.

- Shenkin et al 1986 Essential Trace Element Provision to Patients Receiving Home Intravenous Nutrition in the United Kingdom Clinical Nutrition (1986) 5: 91-97; in their conclusion state: 'All patients receiving home IV Nutrition in the UK receive some form of trace element supplement. In many cases there is also a small oral intake of trace elements as part of the oral diet. Clinical deficiency states for trace elements are therefore uncommon. It is probable that none of the currently available commercial preparations of trace elements is ideal. Zinc provision is too low and usually has to be increased. Copper requirements appear to be variable. Manganese and chromium provision are generally too high. The most common depletion is for selenium.'
- Malone et al 1989 Evaluation of a Trace Element Preparation in Patients Receiving Home Intravenous Nutrition Clinical Nutrition (1989) 8: 307-312. Twenty-four patients (twelve male, twelve female) were included in the study. The mean age was 41.9 years (range 18-62 years) and the mean duration of Parenteral nutrition was 28.1 (range 5-95) months. Most patients had some oral intake.

The study only analysed zinc, copper, manganese, chromium and selenium.

In the discussion the following comments were made:

> *In the present study there was wide variation in serum **zinc** concentration, although most patients, receiving at least 500mcmol zinc per week, had serum zinc concentrations within the reference range. Three individuals with an intake of greater than 400mcmol per week had low serum zinc (less than 10mcmol/L);*
>
> *It can be concluded that 500-700mcmol (zinc) per week is an appropriate level of intake for such patients.*

*The level of **copper** supplement at 20mcmol per day on IVN appeared satisfactory for the majority of patients. The overall mean intake during this study of 10mcmol per day was necessary to correct low serum copper concentration. Since in addition many patients were absorbing some copper from their limited oral intake, it can be concluded that a daily intake of 10- 20mcmol is not excessive.*

*The level of **manganese** supplementation prior to the study was clearly excessive, whereas an input of 5mcmol per bag appears to meet IV requirements more closely.*

*The **chromium** provision in the present study appeared to be excessive and this may be due to an additional effect from chromium contamination of nutrients.*

*Whether chromium should be reduced in the trace element supplement will depend upon whether there are consistent levels of bioavailable chromium in these other solutions. Nonetheless we feel a lower level of Cr supplement would probably be more appropriate.*

*The intake of 0.4mcmol **selenium** per day is known to be at the lower limit of daily requirement. Since most patients commence HPN with impaired selenium status and do not receive supplements every day, they require an increased level of intake until selenium stores have been repleted. We currently recommend 0.8mcmol/day for a period of 1-2 months. Thereafter, the level of 0.4mcmol/day is probably adequate to maintain Status. However, since the response is variable in different patients, monitoring of selenium status is recommended during HPN.*

## 7.3. Xylitol

Intravenous administration is a previously marketed [36] but then prohibited route of administration for xylitol in Australia.

Xylitol is synthesized naturally in humans and animals as part of the glucuronic acid – xylulose cycle - Georgieff et al. (1985) reports that approximately 5 to 15 g of xylitol are synthesized daily in the body, resulting in normal blood levels of xylitol of 0.3 to 0.6 mg/100 mL.

From the Joint FAO/WHO Expert Committee on Food Additives 18-27 April 1977 HO Food Additives Series No. 12 Xylitol:

After both oral and intravenous administration of xylitol subjects showed a fast distribution in the extracellular compartment and the tissues (Bässler et al., 1962). The initial fast distribution phase had a half-life of about four minutes, while the apparent half-life of elimination was approximately 20 minutes (Dixon and East, 1973).

There is an excretion of 10% in the urine after intravenous infusion of xylitol (Bässler, 1965).

Xylitol is mainly metabolized in the liver (80% to glucose only 20%) but a small amount also in kidney, myocardium, erythrocytes, adrenal, brain, lungs and adipose tissue (Bässler, 1965; Hollmann, 1967). Exogenous xylitol can be metabolized in large quantities, intravenously 0.4 gm/kg/hour or 40 g/day orally raises the plasma level to a maximum of 1.5-16 mg/100 ml (Bässler, 1965). The metabolic rate for xylitol is identical in both healthy and diabetic or uraemic patients and patients who suffered from liver diseases (Lang, 1972).

After parenteral administration postoperatively of 10% xylitol solution (1.5 g/kg body weight) Shumer (1971) found a significant increase of lactic acid, uric acid, bilirubin and Alk.Pase in two diabetic and two non-diabetic patients. In a short-term experiment he carried out with two normal volunteers a dosage of 4.5 g/kg during five days produced significant increased levels of urine uric acid, SGOT, SAP, bilirubin, lactic acid, and inorganic phosphate in serum. The levels returned to normal 10 days after cessation of infusion. No effects were found in the BHN, Ca,

[36] Klinit NHS (R) Neopharma, 10%, 20% &50% in 20mL & 500mL ref. 1970-71 Australian Drug Compendium electrolytes and/or calories-intravenous page 166. It was not in subsequent editions

cholesterol, glucose, amino-acids and insulin analyses, urinalyses and haematology were found (Shumer, 1971).

In 1971/1972 oxalate crystals were observed in the kidneys and brain in necropsies performed at the Rafenkrankenhaus in Hamburg on five patients who had received infusions of xylitol. According to the doctors responsible for their treatment they died of the severe conditions from which they had been suffering. These findings gave rise to extensive discussions as to whether xylitol was involved in the causation-of oxalosis.

Xylitol infusion produced no change of blood sugar in normal and a slight increase in diabetic patients. Blood lactate showed a significant increase in the diabetic group but only a slight increase in the normal group. Blood ketone bodies and plasma FFA decreased in both groups after xylitol administration. Plasma insulin increased slightly in five of the normal subjects and in four of the nine diabetic subjects (Yamagata et al., 1967).

In another experiment xylitol was chronically intravenously infused to 12 mildly diabetic patients every morning for seven days. No changes were observed in fasting blood sugar, serum triglycerides, total cholesterol, serum electrolytes or ketone bodies. However, four cases indicated the marked decrease of urine sugar excretion during the experimental period. Xylitol was also given to two diabetic persons with ketosis and decreased the ketone bodies from 5.1 to 0.2 mg % within four hours (Yamagata et al., 1967).

The application is for a recommended maximum daily dose of xylitol 3.0g.

Compared to glucose, insulin secretion"' and hepatic lipogenesis are reduced significantly by xylitol use. Administration of xylitol at a rate of 0.08 to 0.11 g/kg/hr (135-185 g/ day) is accompanied by mobilization of endogenous fat sources and a rise in ketone bodies, so that part of the energy expenditure is recovered by oxidation of fatty acids, acetoacetate, and 0-hydroxybutyrate.[37]

The maximum concentration proposed is concentration of 3% xylitol resulting from a minimum recommended dilution of 100 mL saline/glucose for 10 mL Addaven. When administered as recommended the maximum rate of xylitol would be 0.02 g/kg body weight/h.[38]

## 7.4. Evaluator's conclusions on clinical efficacy for the trace elements

There appears to be a lack of evidence to support the dose of fluoride proposed for this product in Australia. Iodine deficiency has not been reported, presumably because of its rapid absorption from the duodenum as much as from intense monitoring. Otherwise there is support for the inclusion of the other elements as they have been used in prevention and treatment of deficiency states.

The doses proposed are in general supported by at least one guideline (AuSPEN, ASPEN or ESPEN). The only concern being for Mn2+ where the ESPEN guide recommends a higher dose which then raises concerns with regard to toxicity. Some of the trace elements are not supported by the ASPEN guidelines based on what is perceived in them as inadequate evidence.

[37] Georgieff et al., (1985)
[38] Page 47 clinical overview

**Table 4: Summary comparison of Addaven, recommended daily dose (and source), supporting evidence, deficiency and toxicity.**

| Trace element | Addaven Content | | Recommended daily dose | Supporting Evidence | Deficiency on TPN | Effects of deficiency | Toxicity |
|---|---|---|---|---|---|---|---|
| | mcmol | mg | | | | | |
| $Cr^{3+}$ | 0.2 | 0.01 | 0.010-0.015mg/d[a,c,g] | Balance studies Autopsies | Yes Responds | Carbohydrate and lipid metabolism affected, neuropathy | None reported with chromium chloride[b] |
| $Cu^{2+}$ | 6.0 | 0.38 | 0.3–0.5mg/d[a,c,g] | Balance studies Autopsies | Yes Responds | Hypochromic anaemia, neutropenia or pancytopenia | None reported[b] Possible liver damage concern |
| $Fe^{3+}$ | 20 | 1.10 | 1.1mg/d[e] 1-1.2mg/d[g] | Balance & tolerance studies Autopsies | Yes Responds | iron deficiency anaemia | Possible infection risk[d] |
| $Mn^{2+}$ | 1 | 0.055 | 0.055mg/d[a,c] 0.2-0.3mg/d[g] | Balance studies Autopsies | Yes x 1 Responds | Child had short stature, abnormal bony metaphysis and diffuse bone demineralization. (Involved in multiple enzymes including arginase, glutamine synthetase, and manganese superoxide dismutase) | Abnormal midbrain MRI images, some memory loss with muscle weakness, signs suggestive of Parkinsonism |
| $I^-$ | 1 | 0.13 | 0.13mg/d[e] 0.1mg/d[g] | Based on oral balance and absorption studies | Not reported | Described clinically otherwise | None reported Both hyperthyroidism and hypothyroidism described clinically |
| $F^-$ | 50 | 0.95 | 1mg/d[e,f,g] | No supporting data | Not reported | Described clinically otherwise | None reported Described clinically |
| $MoO_4^{2-}$ (as $Mo^{6+}$) | 0.2 | 0.019 | 0.02mg/d[e,g] 0.019mg/d[c] | Balance studies Limited data | Yes x 1 Responds | Progressive tachycardia, tachypnoea, neurological and visual changes, and eventually coma; reduced activity of sulphite oxidase and xanthine oxidase | None reported |
| $SeO_3^{2-}$ (as $Se^{4+}$) | 1 | 0.08 | 0.06-0.1mg/d[a,c] 0.02-0.06mg/d[g] | Balance studies Autopsies | Yes Responds | Nail and hair changes skeletal muscle myopathy reversible and fatal cardiomyopathy. | None reported Described clinically: Nausea, vomiting, hair loss, irritability, fatigue, and a peripheral neuropathy |
| $Zn^{2+}$ | 77 | 5.0 | 2.5-5mg/d[a,g] 3.2-6.5mg/d[f] | Balance studies Autopsies | Yes Responds | eczematous rash, nail changes, alopecia, mental apathy and depression, visual dysfunction, and impaired immune function | Few cases hypotension, pulmonary oedema, diarrhoea, vomiting, jaundice, and oliguria |

[a] ASPEN recommended; [b] Despite raised serum and tissue levels in some patients; [c] AuSPEN recommended; [d] Postulated related to saturation of transferrin; [e] ASPEN, not routinely added in US; [f] AuSPEN no recommended dose; [g] ESPEN recommended.

# 8. Clinical safety

## 8.1. Adverse events

There were multiple AEs reported in the literature, virtually all considered not related to the parenteral nutrition - the following being examples:

- Santos et al 2001 bacteraemia in 2/10, a four-fold increase from baseline in serum triglycerides in 1/10.
- Garcia-de-Lorenzo et al 2005 (burns patients) septicaemia or documented infections 6/22, death from multiple organ failure 7/22 usually with a pre-existing severe sepsis, hyperglycaemia at baseline, abnormal hepatic changes.
- Jacobson and Wester 1977 No adverse clinical effects of any kind in 4 patients.
- Zhang et al 2007 Hyperglycaemia 23/48, infection5/4, oedema 1, fever 1, tetter 1.

## 8.2. Adverse reactions

Limited information is available:

- Santos et al 2001 There were no side-effects attributable to PN.
- Garcia-de-Lorenzo et al 2005 Although no significant difference in global safety was found between lipid emulsions, a statistically higher number of patients experienced liver function abnormalities with MCT/LCT.
- Jacobson and Wester 1977 No adverse clinical effects of any kind in 4 patients.
- Zhang et al 2007 using Addamel said adverse events not related to the trial drug (growth hormone), 5 placebo-treated patients experienced mild electrolytes imbalance.

## 8.3. Toxicity of single trace elements

### 8.3.1. Chromium

Renal impairment reported with oral chromium picolinate supplements, but none with chromium chloride. The former is renally excreted; therefore of concern in patients with poor renal function.

### 8.3.2. Copper

Acute toxicity results in abdominal symptoms, liver and kidney failure, coma, and death.

Chronic copper toxicity, as occurs in Wilson's disease, results in accumulation in the liver, kidneys, brain and cornea leading to hepatic necrosis and cirrhosis, renal failure, and neurologic disorders.

For patients with cholestasis a risk of copper overload exists during long-term PN.

### 8.3.3. Fluoride

Acute excessive fluoride may lead to death. Chronic toxicity of fluoride may involve teeth and bone structures.

### 8.3.4. Iodide

Iodine toxicity is rare, most people being tolerant to excess provision.

### 8.3.5. Iron

Excessive body iron may accumulate as hemosiderin in iron stores and the reticuloendothelial system in cells of any organ. Typical symptoms of primary as well as secondary haemochromatosis comprise hepatic cirrhosis, diabetes mellitus, and hyperpigmentation of the skin that may be combined with other symptoms such as cardiac arrhythmias or arthropathy.

### 8.3.6. Manganese

There have been reports of toxicity due to overprovision of manganese during PN, this is of concern especially in patients with chronic liver disease. Abnormal midbrain MRI images, some memory loss with muscle weakness, signs suggestive of Parkinsonism have been reported.

### 8.3.7. Selenium

Exposure to chronic excess, known as selenosis, causes hair and nail changes, gastrointestinal upsets, and nervous system abnormalities. Acute toxicity is rare, and can be fatal. There have been no reports of selenium toxicity during PN.

### 8.3.8. Zinc

Acute toxicity may result in epigastric abdominal pain, nausea, vomiting and diarrhoea. Chronic toxicity may lead to decreased serum copper levels, neutropenia, reduced high-density lipoprotein, and impaired immune function.

### 8.3.9. Molybdenum

There is little data on toxicity of molybdenum in man.

## 8.4. Overdose

Cases of zinc overdose with PN have been reported:

- One case showed initial symptoms of hypotension, pulmonary oedema, diarrhoea, vomiting, jaundice, and oliguria showed fluctuating progress. Poor renal function made haemodialysis necessary and eventually led to death.
- In seven patients, the zinc overdose led to reversible hyperamylasaemia with no clinical signs of pancreatitis.

In the post marketing information 3 patients received an overdose: one patient developed paraesthesia as potassium was administered (a serious case, from which the patient recovered), the second patient developed injection site pain and in the third patient no adverse drug reaction occurred.

## 8.5. Post-marketing experience

As Addaven has only very recently been marketed (first supply in Sweden in October 2014), no evidence is available of safety concerns from use of Addaven.

### 8.5.1. PSURs

These are for Addamel N 1986 to 31 December 2014. Not all are felt due to this preparation.

Serious ARs:

- Anaphylactoid reaction in a [information redacted] with short bowel disease 9 hours after start of PN. Doctors believed that the Intralipid component of the PN regimen was the causative agent. The [information redacted] made a full recovery.
- A [information redacted] received Addamel N as a part of an PN regimen. Cardiac palpitations (serious) and headache (non-serious) occurred almost immediately after start of the infusion at the fifth day of the daily PN treatment. The patient felt better 4 hours after discontinuation of the infusion (outcome recovered). The fat emulsion was possibly broken, which may affect the pharmaceutical quality.
- Tachycardia in a [information redacted] with hypoxic brain damage, diabetes, and respiratory arrest in the medical history. The tachycardia occurred on the same day as the treatment with PN. The patient recovered with sequelae.
- An [information redacted] with an extensive medical history, who received PN regimen, experienced anaphylactic shock, vomiting, hypotension, and unconsciousness. The outcome was unknown.
- Administration site reaction (vessel perforation and inflammation at site of injection) with plausible temporal relationship in a [information redacted] patient under PN regimen. The outcome was reported as not recovered.
- Septicaemia three hours after PN infusion was reported for a [information redacted] with medical history of breast cancer, peritoneal metastases, transverse colectomy and entero-cutaneous fistula who made a full recovery.

## 8.6. Xylitol

Intravenous administration of xylitol can produce metabolic acidosis, and a number of effects including diuresis, oliguria, azotaemia, acidosis, hepatic disturbances and hyperuricaemia, as well as renal and cerebral toxicity related to deposition of oxalate crystals in the brain, kidney[39] and other organs. Thomas reviewed the histories of 22 patients. Possible adverse reactions (7 patients)[40] were associated with total doses averaging 485g and mean infusion of 0.32g/kg/h. A mean total dose of 1,098g and mean infusion rate 0.49g/kg/h resulted in definite adverse reactions.

[39] Deposits of oxalate crystals in the tissues particularly in the kidneys were noted for the first time with xylitol infusion in Australia Thomas, D. W., Edwards, J. B., Gilligan, J. E., Lawrence, J. R., Edwards, R. G.: Complications following intravenous administration of solutions containing xylitol. Med. J. Aust. 1, 1238-1246 (1972). 'These findings formed the basis of an Adverse Drug Reaction Report to the Australian Drug Evaluation Committee. Subsequently, xylitol was withdrawn from clinical use.'

[40] Three of these patients only one possible adverse reaction, one patient developed three possible adverse reactions, and three further patients showed four possible adverse reactions.

Deaths or serious adverse events have been reported with doses of ≥ 150 g xylitol per day for more than 4 days (≥ 2.5 g/kg body weight/day) with total doses generally in excess of 1 kg. No adverse effects have been reported at intravenous doses of xylitol up to 50g/day.

The toxicity of xylitol appears to be related to the rate of administration and solution concentration as well as the total dose. Adverse events were not noted in patients administered xylitol at a rate of 0.125 - 0.25g/kg/h, depending on the concentration, and an upper limit for safe xylitol administration has been given as 210g/day at a rate of 0.125g/kg body weight/h.

In a study in which 100g of xylitol was administered at a rate of 0.25-0.5 g/kg BW/h in a concentration of 10% reported increases in serum lactate, pyruvate, urate and bilirubin compared to glucose administration (Kortilla and Mattila 1979).

The maximum concentration proposed is a concentration of 3% xylitol resulting from a minimum recommended dilution of 100 mL saline/glucose for 10mL Addaven. When administered as recommended the maximum rate of xylitol would be 0.02g/kg body weight/h.[41]

Increased urinary oxalate excretion and precipitation of calcium oxalate crystals has been reported in brains, kidneys and hearts after very high doses of xylitol (> 100 g/d) to humans (Ludwig et al., 1984, Leidig et al., 2001, Heye et al., 1991, Schultze et al., 1983).[42]

The guidelines for Parenteral nutrition do not recommend the use of the sugar substitute xylitol. Its use is still controversial because of possible hepatotoxicity or nephrotoxicity.[43]

This study found adverse events considered attributable to Parenteral nutrition containing xylitol did not appear to occur. The study only included 55 patients and was unable to show any differences from historical controls.

When administered in larger amounts, xylitol is associated with a pattern of adverse events including metabolic acidosis, hepatotoxicity and renal and cerebral disturbances (Thomas et al., 1972, Thomas et al., 1972b, Leidig et al., 2001, Schultze et al., 1983). At even higher doses (≥150 g/d with total doses in excess of 5 kg), deaths have occurred resulting primarily from damaged caused in the brain and kidney by deposition of oxalate crystals (Heye et al., 1991, Ludwig et al., 1984, Buttner et al., 1987).

From a 1970 TGA letter:

> *By January 1970 a further six cases of acidosis following xylitol administration had been reported, including three deaths (i.e. 6 deaths total at that time).*
>
> *Since then we have received retrospective reports of a further ten adverse reactions to Xylitol infusion which occurred before its withdrawal from the market.*
>
> *In the opinion of our own chemist if there is a toxic contaminant it could also be any of a thousand other compounds.*
>
> *In most cases batch number were not able to be ascertained.*[44]

## 8.7. Evaluator's overall conclusions on clinical safety

Based on the evidence provided, the safety concerns relating to the use of the product as proposed are limited to some of the individual elements.

Manganese toxicity has occurred long term with previous recommended dosage. It has been reduced in this preparation which has been in use for only a short period of time.

[41] Page 47 clinical overview
[42] 2.4 Non-Clinical Overview (Xylitol) page 6
[43] Assessment of xylitol serum levels during the course of parenteral nutrition including xylitol in intensive care patients: A case control study Schneider et al Clinical Nutrition xxx (2013) 1-6
[44] page 114 file 1970/00961

Renal and Liver dysfunction will affect the excretion of some of the elements with potentially toxic effects that may compound the dysfunction.

The required doses of some of the elements will vary with local environment and practices within Australia as well as country of origin: $I^-$ being low in Tasmania and NZ, $Se^{++}$ being low in NZ, $F^-$ varying across Australia.

For all these reasons intense monitoring is required. While this is likely to occur for patients needing long term TPN or PN, it is unlikely to occur in routine post- surgical use of short term PN unless there are existing abnormalities of trace elements known or suspected.

The use of intravenous xylitol was prohibited on the advice of ADEC. It has been accessed under the SAS. The sponsor has chosen to submit the evidence for it in the non-clinical section.[45]

'The causality was proven beyond doubt linking xylitol metabolism with a syndrome consisting of diuresis, oliguria, uraemia, hyperuricaemia, hyperuricosuria, lactic acidosis and excessive Oxl production, resulting in Ca Oxl crystal deposition in various tissues including brain (Conyers *et al*. 1985).'[46]

The proposed dose and rate of administration appears to be well below that causing toxicity.

# 9. First round benefit-risk assessment

## 9.1. First round assessment of benefits

The claimed benefits of Addaven in the proposed usage are:

- Prevention of deficiency states.
- Correction of mild deficiency states.
- The doses proposed are in general supported by at least one guideline (AuSPEN, ASPEN or ESPEN).

### 9.1.1. Prevention of deficiency states

This is only relevant in long term parenteral nutrition and then it may be unnecessary depending on the amount of associated enteral nutrition possible. The need for supplementation of total parenteral nutrition with trace elements is well established.

### 9.1.2. Correction of mild deficiency states

The problem is to define a mild deficiency state. Marked deficiency is obvious and would require additional trace element, mild deficiency is more likely to be suspected based on history, particularly as plasma levels often do not reflect body stores.

### 9.1.3. The doses proposed are in general supported by at least one guideline (AuSPEN, ASPEN or ESPEN)

The exception to this is fluoride, which is at a level previously used for a long time in Addamel N, but is not supported by any guideline.

This evaluator sees that this formulation goes to meet the AusPEN Recommendations for Industry:

[45] Further safety data is available from clinical studies in which xylitol has been administered intravenously as part of PN as an energy source – either as a replacement for glucose or in combination with glucose and/or other carbohydrates. These studies have also been identified via a systematic literature search (the search details also approved and included) and are included in the non-clinical modules, since they do not relate to clinical use of Addaven and therefore do not fit into the clinical sections of the dossier.

[46] R11 524245 Xylitol - Prohibited Imports - Nonclinical Safety Assessment 24 November 2011.

*To support safe and evidence based clinical care, new multi-trace elements products that reflect the present recommendations are required to be available on the Australian and NZ market.*

## 9.2. First round assessment of risks

The risks of in the proposed usage are:

- The supporting evidence is very limited.
- There appears to be a lack of evidence to support the dose of fluoride proposed (the AusPEN guidelines do not support its presence).
- There is concern with respect to manganese where the ESPEN guidelines recommends considerably higher dose which raises concerns regarding toxicity.
- Some of the trace elements are not supported by the ASPEN guidelines based on what is perceived in them as inadequate evidence.
- The sponsor argues that the previous formulation has been used for a long time; however, this formulation was only first marketed in Sweden in October 2014.

## 9.3. First round assessment of benefit-risk balance

Based on the usual process of assessment, the evaluator considers the benefit-risk balance of Addaven given the proposed usage, is unfavourable.

*Comment: It may be that different criteria are needed in this case.*

The following quote from the AusPEN guidelines is relevant:

*First, there is a paucity of research in the area of trace elements provision in Parenteral nutrition. The majority of the available literature is 20 to 40 years old, and due to the changes in Parenteral nutrition practices in this time it is currently unknown to what degree it can now be generalised to the modern Parenteral nutrition context. Second, with few exceptions, the research has been conducted outside of Australia and NZ and therefore the impact of different solutions, practices and this region's vulnerability to lower baseline trace elements levels, such as Se and I, limit the degree to which these results can be applied to our population, although this has been extrapolated from local population information when possible. Third, the realities of nutritional research in which the elements of well-designed randomised controlled trials, notably blinding and randomisation, are not always possible due to ethical or logistical reasons limits the high level evidence available in this field. While high levels of evidence are sought to justify changes to clinical practice, lower grades of evidence often represent the best level of evidence available and this does not necessarily invalidate the recommendations.*

Because of the sponsor's repeated referral to Addamel N as a source, the evaluator looked to a previous evaluator's assessment of the product:

*The central questions relate to the extent to which it has been established that the combination will meet clinical requirements (a) in terms of adequacy, and (b) in terms of non-toxicity. For example, what proportion of TPN patients treated with the product required further supplementation, in various clinical circumstances (relating to renal or hepatic function, surgical wounds, metabolic rate, etc.)? What proportion of such patients develop (or threaten to develop) hazardous levels of one or more of the trace elements included in the product? It seems little information on this is available from the published literature.*

*As noted [in] this report, no pharmacokinetic data were presented in the expert report.*

*Unless the dosage range for each is broad, it would seem unlikely that a fixed combination of 9 active substances would provide an adequate intake for each without exceeding the safe level for any. Judging from the expert report, this problem is by no means purely hypothetical, and routine monitoring would be required. It is likely that, based on such monitoring, further supplementation of some trace elements would be required, possibly combined with reduction in the dose of the fixed combination product if its administration was to be continued.*

*Rather than use a fixed combination of trace elements, it would be preferable in my opinion to assess each patient individually and prescribe trace elements in amounts which appear appropriate.*

*I therefore recommend refusal of the application.*

The date of the clinical evaluation report was 5 October 2005 (data submitted 2 November 2004).

*Comment: This current submission contains ~20 Parenteral nutrition articles since the date of the previous submission and 8 new guidelines.*

# 10. First round recommendation regarding authorisation

Authorisation is not recommended.

- It fails to meet some of the requirements of a literature based submission:

  *Under exceptional circumstances, a LBS (including a mixed application) may be accepted for the registration of a new chemical entity (NCE) in Australia where it has been marketed in other countries for many years.*

- The sponsor argues for the drug being a new formulation of a pre-existing preparation Addamel N.

  *We will not accept a LBS (or a mixed application) for applications to register a NCE where the marketing in other acceptable countries has been less than ten years, except where:*

  – *the NCE has been designated in Australia as an Orphan Drug, or*

  – *there is no medicine registered or available in Australia that is registered for the same or (in the view of the TGA) essentially the same indication.*

  *A previous submission of Addamel N claimed orphan status, but not this submission for Addaven. There are alternatives for many of the components.*

- There exists a current ADEC recommendation to prohibit the use of one of the components: Xylitol.

# 11. Clinical questions

Not applicable.

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au  Phone: 1800 020 653  Fax: 02 6232 8605
https://www.tga.gov.au