



**Australian Government**

**Department of Health**

Therapeutic Goods Administration

# Australian Public Assessment Report for nine trace elements including chromic chloride

Proprietary Product Name: Addaven

Sponsor: Fresenius Kabi Australia Pty Ltd

**March 2017**

## 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 AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

### Copyright

© Commonwealth of Australia 2017

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <[tga.copyright@tga.gov.au](mailto:tga.copyright@tga.gov.au)>.

# Contents

|  |           |
|--|-----------|
| <b>About AusPARs</b>   | <b>ii</b> |
| <b>Common abbreviations</b>                                      | <b>4</b>  |
| <b>I. Introduction to product submission</b>                     | <b>6</b>  |
| Submission details   | 6         |
| Product background   | 6         |
| Regulatory status  | 8         |
| Product Information  | 8         |
| <b>II. Quality findings</b>                                      | <b>8</b>  |
| Drug substance (active ingredient)                               | 8         |
| Drug product   | 9         |
| Biopharmaceutics   | 9         |
| Quality summary and conclusions                                  | 10        |
| <b>III. Nonclinical findings</b>                                 | <b>10</b> |
| Pharmacology   | 10        |
| Pharmacokinetics   | 10        |
| Toxicology   | 11        |
| Nonclinical summary and conclusions                              | 14        |
| <b>IV. Clinical findings</b>                                     | <b>15</b> |
| Pharmacokinetics   | 16        |
| Pharmacodynamics   | 16        |
| Dosage selection for the pivotal studies                         | 17        |
| Efficacy   | 17        |
| Safety   | 17        |
| First round benefit-risk assessment                              | 18        |
| First round recommendation regarding authorisation               | 20        |
| Clinical questions   | 21        |
| <b>V. Pharmacovigilance findings</b>                             | <b>21</b> |
| Risk management plan   | 21        |
| <b>VI. Overall conclusion and risk/benefit assessment</b>        | <b>25</b> |
| Risk-benefit analysis  | 25        |
| Outcome  | 31        |
| <b>Attachment 1. Product Information</b>                         | <b>32</b> |
| <b>Attachment 2. Extract from the Clinical Evaluation Report</b> | <b>32</b> |

## 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 <sub>t1-t2</sub> | area under the plasma drug concentration-time curve from t1 to t2 |
| AuSPEN               | AustralAsian Society for Parenteral and Enteral Nutrition         |
| C <sub>max</sub>     | 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   |
| LBS                  | literature based submission                                       |
| 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   |
| $t_{1/2}$    | elimination half life                                |
| TE           | trace elements                                       |
| Tmax         | Time taken to reach the maximum concentration (Cmax) |
| TPN          | Total Parenteral Nutrition                           |
| Zn           | zinc   |

## I. Introduction to product submission

### Submission details

|                                    |  |
|------------------------------------|--|
| <i>Type of submission:</i>         | New chemical entity  |
| <i>Decision:</i>                   | Approved   |
| <i>Date of decision:</i>           | 26 July 2016   |
| <i>Date of entry onto ARTG</i>     | 29 July 2016   |
| <i>Active ingredients:</i>         | Nine trace elements: Chromic Chloride, Cupric Chloride Dihydrate, Ferric Chloride Hexahydrate, Manganese Chloride, Potassium Iodide, Sodium Fluoride, Sodium Molybdate Dihydrate, Sodium Selenite and Zinc Chloride  |
| <i>Product name:</i>               | Addaven  |
| <i>Sponsor's name and address:</i> | Fresenius Kabi Australia Pty Ltd<br>2/2 Woodland Way<br>Mount Kuring-Gai NSW 2080  |
| <i>Dose form:</i>                  | Concentrated Injection   |
| <i>Strengths:</i>                  | Chromic Chloride 53.3 µg, Cupric Chloride Dihydrate 1.02 mg, Ferric Chloride Hexahydrate 5.40 mg, Manganese Chloride 198 µg, Potassium Iodide 166 µg, Sodium Fluoride 2.10 mg, Sodium Molybdate Dihydrate 48.5 µg, Sodium Selenite 173 µg and Zinc Chloride 10.5 mg in 10 mL |
| <i>Container:</i>                  | Polypropylene ampoule  |
| <i>Pack size:</i>                  | 20 x 10 mL ampoules  |
| <i>Approved therapeutic use:</i>   | To meet basal to moderately increased requirements of trace elements in parenteral nutrition in adults, when either oral or enteral nutrition is inappropriate   |
| <i>Route of administration:</i>    | Intravenous  |
| <i>Dosage:</i>                     | The maximum recommended daily dose is 10 mL (that is, one ampoule). If treatment is continued for more than 4 weeks, monitoring of trace element levels in plasma, especially manganese, is required.  |
| <i>ARTG number:</i>                | 244493   |

### Product background

This AusPAR describes the literature based submission by Fresenius Kabi Australia Pty Ltd to register Addaven as a new chemical entity. Addaven is a product for single use only and contains nine trace elements (TE) as the active ingredients, which are all considered

to be simple inorganic salts. Addaven is a fixed combination of TE in amounts normally absorbed from the oral diet. Patients receiving parenteral nutrition without adequate TE provision have shown deficiency of several TE.

The proposed indication is:

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

Neither concentrated nor ready-to-use parenteral products only containing trace elements as active ingredients are currently registered in Australia. However, Fresenius Kabi has globally supplied electrolyte and trace element solutions intended as additives in parenteral nutrition for many years, commencing with “Addamel” in 1975. At the time, “Addamel” contained the estimated daily supply of calcium, magnesium, iron, zinc, manganese, copper, fluoride and iodide. The trace element solution “Addamel N” was subsequently developed by the sponsor following revision of the recommendations for essential trace elements. In addition to the TE included in “Addamel”, “Addamel N” contains selenium, molybdenum and chromium; furthermore, the electrolytes have been removed from the formulation. “Addamel N”, which has been marketed since 1986 and is currently registered in 47 countries (see below) under different trade names, has proven to be a well-tolerated product which can be safely administered within the recommended dosages.

Addaven is an updated version of “Addamel N” in which the concentration of copper, manganese and zinc has been decreased and the concentration of selenium has been slightly increased. No significant changes have been made to the pharmaceutical properties of the product; hence, Addaven has the same physicochemical properties as “Addamel N” and meets the same requirements as regards quality and clinical indication. Neither have any changes been made to the manufacturing process or the container closure system; Addaven is intended to be used in the same way, and have the same effect, as the previously provided trace element products. Addaven differs from Addamel N in the concentration of four constituents that have been updated in alignment with current recommendations.

Table 1 shows a comparison of the “Addamel”, “Addamel N” and “Addaven” formulations.

**Table 1: TE concentration in the Addamel products and Addaven (in 10 mL).**

|            | Addamel |        | Addamel N* |        | Addaven |        |
|------------|---------|--------|------------|--------|---------|--------|
|            | [mg]    | [µmol] | [mg]       | [µmol] | [mg]    | [µmol] |
| Chromium   | -       | -      | 0.01       | 0.2    | 0.01    | 0.2    |
| Copper     | 3.1     | 5.0    | 1.24       | 20.0   | 0.4     | 6.0    |
| Fluorine   | 0.95    | 50.0   | 0.95       | 50.0   | 0.95    | 50.0   |
| Iodine     | 0.13    | 1.0    | 0.13       | 1.0    | 0.13    | 1.0    |
| Iron       | 2.7     | 50.0   | 1.1        | 20.0   | 1.1     | 20.0   |
| Manganese  | 2.2     | 40.0   | 0.275      | 5.0    | 0.055   | 1.0    |
| Molybdenum | -       | -      | 0.019      | 0.2    | 0.019   | 0.2    |
| Selenium   | -       | -      | 0.03       | 0.4    | 0.08    | 1.0    |
| Zinc       | 1.3     | 20.0   | 6.5        | 100.0  | 5.0     | 77.0   |

\* Addamel N is also marketed under the trade names of Additrace, Tracel, and Addamel Novum

The concentrated injection is indicated to meet basal to moderately increased requirements of trace elements in parenteral nutrition. The maximum recommended daily dose is 10 mL (that is, one ampoule). If treatment is continued for more than 4 weeks, monitoring of TE levels in plasma, especially manganese, is required.

### **Regulatory status**

At time of submission, the product had been approved for use in a number of EU countries, and also Switzerland and New Zealand. Addaven had not yet been submitted in the US or Canada. Addaven was submitted in the UK on 21 February 2013, and subsequently withdrawn on 15 December 2015 due to internal business reasons. Addamel N has been approved in the UK since May 1999 and is currently being marketed.

### **Product Information**

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **II. Quality findings**

### **Drug substance (active ingredient)**

Each of the nine active ingredients is a simple inorganic salt, for which:

- Ferric chloride hexahydrate and sodium molybdate dihydrate is each the subject of a European Pharmacopoeia (Pharmacopoeia Europaea, Ph Eur) (Monographs 01/2008:1515 and 01/2008:1565, corrected 6.3, respectively), but is not the subject of a United States Pharmacopoeia (USP) monograph.
- Chromic chloride, cupric chloride and manganese chloride is each the subject of a USP monograph, but is not the subject of a Ph Eur monograph.
- Potassium iodide, sodium fluoride and zinc chloride is each the subject of a Ph Eur monograph (Monographs 01/2008:0186, corrected 6.0, 01/2008:0514 and 01/2008:0110, corrected 6.6, respectively), and is also described in the USP.
- Sodium selenite (anhydrous) is not described in a monograph in either pharmacopoeia; however, sodium selenite pentahydrate is the subject of a Ph Eur monograph (Monograph 01/2008:1677), but is not the subject of a USP monograph.

The drug substances are manufactured from inorganic salts by simple achiral procedures.

True or pseudo-polymorphism of the drug substances is irrelevant to the dosage form, as is the BCS Class of each.

No limits are applied to the particle size distribution of the drug substance; this has been accepted given that the active pharmaceutical ingredient (API) is in aqueous solution in the finished product.

With the exception of sodium selenite, the impurities controlled in the drug substances are those specified in the relevant Ph Eur or USP monograph. The sodium selenite specification includes all relevant tests and limits stipulated in the Ph Eur monograph for Sodium Selenite Pentahydrate, with addition of tests for Total Aerobic Microbial Count (TAMC) and Total Yeasts and Moulds Count (TYMC) plus in-house tests for Carbonates and Loss on Drying.



No issues relating to the quality control of the drug substances were raised with the applicant.

### **Drug product**

The finished product is a clear solution essentially free from visible particles, with a degree of coloration ranging from almost colourless to  $\leq$  Y5 (slightly yellowish). The osmolality of the solution is approximately 3100 mOsm/kg water and the density is 1.098 g/cm<sup>3</sup>. The pH of the solution before terminal steam sterilisation is adjusted to approximately 2.4-2.5 in order to avoid precipitation and to decrease the reduction of the iodine content observed during sterilisation of "Addamel N".

An overage of 20% of potassium iodide is added at manufacture to compensate for irreversible losses of iodine that occur during manufacture. The loss of iodine is not associated with degradation or formation of impurities, since iodine at the stated conditions remains stable. The two main causes for the loss of iodine are irreversible adsorption of I<sub>2</sub> to the ampoule and by evaporation into the ampoule head space. As the total concentration of iodine is very low, even a very modest adsorption can account for the observed effects. Further, the vapour pressure of the volatile I<sub>2</sub> increases rapidly with increasing temperature (0.05 kPa at 25 °C → 0.13 kPa at 40 °C) and the evaporation will thus increase during the sterilisation process.

Sorbitol was originally included in "Addamel N" to prevent precipitation at sterilisation and during storage. Due to risks for patients with hereditary fructose intolerance, other stabilisers were later tested to replace sorbitol, and xylitol was found to be appropriate as it is safe, well characterised and gives clear solutions that remain clear and without precipitate after heat sterilisation.

The concentrated solution is supplied in ampoules with a twist-off sealing that are blow moulded from polypropylene resin, filled with solution and sealed using the Blow-Fill-Seal (BFS) technique. In order to offer a user-friendly product the ampoules are supplied, which contributes to a smooth opening. The luer lock integrated in the ampoule neck, combined with the ampoule's almost complete tendency to collapse, offers the possibility to fill a syringe without introducing unsterile air into the container.

The release and expiry specifications for the finished product (as amended following TGA action) are satisfactory.

No degradants arising from the active ingredients are present in the finished products, and an acceptable justification was given for not monitoring degradative impurities arising from the xylitol excipient in the finished product.

The stability data support a shelf life of 24 months stored below 30°C in the polypropylene ampoules described above.

The compatibility of Addaven with emulsions of amino acids, lipids and glucose used for TPN has been inferred from the compatibility of "Addamel N" with 15 standard commercially available admixtures stored in infusion bags or 3-chamber bags at 2-8°C for 6 days, followed by 24 h at 25°C.

Sterility and safety-endotoxins aspects of the submission have been evaluated independently, and are acceptable.

### **Biopharmaceutics**

No bioavailability data are required as the product, after dilution, is a simple aqueous solution that is given by intravenous infusion in an admixture with emulsions of amino acids, lipids and glucose used for Total Parenteral Nutrition (TPN).

## Quality summary and conclusions

There are no objections to registration from a Quality perspective.

## III. Nonclinical findings

Addaven consists of a number of trace elements, with xylitol as an excipient. The maximum daily doses for all trace elements in Addaven (that is, chromium, copper, iron, manganese, iodine, fluoride, molybdenum, selenium and zinc) are either below those conferred by other registered TPN or TPN supplementation products, below the permitted daily exposures (PDEs) listed in published guidelines<sup>1</sup> or are below the predicted dietary intake (taking into account the extent of absorption from the intestinal tract). Therefore, the proposed daily doses of the trace element components of Addaven are acceptable from a toxicological perspective. This nonclinical evaluation focussed on xylitol, considered to be a new excipient for this route of administration (IV), though the substance has had a chequered history in Australia.

The submission consisted of literature references to address the safety of the trace element or xylitol components of Addaven. None of the studies were conducted with Addaven, but toxicological interactions between the trace elements at the proposed (therapeutic) concentrations and xylitol are considered unlikely. The overall quality was acceptable for the nature of this product (most components with a long history of use). Additional published papers were sourced by the nonclinical evaluator.

## Pharmacology

### Primary pharmacology

No primary pharmacology studies were submitted.

### Secondary pharmacodynamics and safety pharmacology

Insulin production from a xylitol infusion was lower than that observed with a glucose infusion in rats, monkeys and humans. A different pattern was seen in rabbits and dogs; in both species, significant insulin production was observed following a xylitol infusion.

No safety pharmacology studies with xylitol were submitted.

## Pharmacokinetics

Following IV administration, the plasma half-life of xylitol is relatively short (19-31 min in human subjects). The turnover of xylitol is 0.66-0.72 g/kg/h or 11-12 mg/kg/min.<sup>2</sup> The oral bioavailability of xylitol ranges from 49-95%,<sup>3</sup> but the rate of absorption from the GI tract is slow (0.2-0.4 g/kg/h).<sup>4</sup> Both of these factors need to be considered when extrapolating data from oral studies to the IV route.

---

<sup>1</sup> International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Guideline for Elemental Impurities Q3D", 16 December 2014.

<sup>2</sup> Demetrakopoulos GE, Amos H. Xylose and xylitol: metabolism, physiology and nutritional value. *Wld. Rev. Nutr. Diet.* 32: 96-122 (1978); Igarashi T. Infusion Velocity and Tolerance of xylitol solution. *Journal of Nutritional Science Supplement* 11: 20-28 (1971).

<sup>3</sup> Asano T, Levitt MD, Goetz FC. Xylitol absorption in healthy men. *Diabetes* 22: 279-281 (1973).

<sup>4</sup> Grenby TH. *Advances in Sweeteners*. Chapman & Hall, London (1996).

Xylitol is predominantly metabolised in the liver, with a small amount of metabolism in the kidney.<sup>5</sup> The major pathway of xylitol metabolism involves conversion to D-xylulose which is phosphorylated to xylulose-5-phosphate, an intermediate of the pentose phosphate pathway, where it is metabolised to fructose-6-phosphate and glyceraldehyde-3-phosphate. The bulk of the carbon from xylitol enters the glycolytic/gluconeogenic pathway at the level of fructose-6-phosphate. The main product of xylitol metabolism is glucose, most of which accumulates as glycogen.<sup>6</sup> Blood glucose is not appreciably increased. The glycogen phosphorylase reaction requires vitamin B6 as a cofactor.

A minor pathway of xylitol metabolism involves phosphorylation of xylulose by fructokinase (to generate xylulose-1-phosphate), leading to the formation of dihydroxyacetone phosphate and glycoaldehyde, the latter is a known precursor of oxalate.<sup>7</sup> Oxalate was shown to be produced at significant levels in hepatic samples from rats and humans but not from rabbits.

Based on metabolic parameters (oxalate production in liver samples and in vivo plasma insulin responses), rats appear to be the more appropriate species for toxicity studies of rabbits.

## Toxicology

### General toxicity

The general toxicity of IV administered xylitol was examined in a series of single dose (standard study design) and repeat dose toxicity studies (up to 5 weeks in duration) in mice, rats and rabbits. Several single dose toxicity studies were conducted in an attempt to understand the adverse effects (jaundice, elevated liver enzymes and oxalate deposition in kidneys and midbrain) observed in human subjects that had received IV infusions of xylitol in the late 1960s-early 1970s. The overall quality of the studies was reasonable. The data are considered acceptable when taking into account the generally safe profile of orally administered xylitol (an Acceptable Daily Intake (ADI) has not been set by the Joint FAO/WHO Expert Committee on Food Additives (JECFA))<sup>8</sup> for xylitol; a no-effect oral dose in human subjects was considered to be ~0.4 g/kg, ~3 times the xylitol dose from Addaven, taking into account oral bioavailability.<sup>9</sup>

The liver was the main target organ for toxicity in mice and rabbits. Elevated serum liver enzymes (ALT, AST) and bilirubin, and histopathological changes in the liver (single cell necrosis, focal necrosis, liver hypertrophy) were observed in one or both species at high doses or high infusion rates. A mechanistic study in rabbits indicated that liver damage only occurred if the xylitol infusion rate exceeded the elimination rate; evidence of liver damage was apparent at infusion rates >1 g/kg/h compared with a xylitol turnover rate of 0.7 g/kg/h. In clinical cases where adverse effects were observed, the infusion rate of xylitol was up to 1 g/kg/h compared with a turnover rate of ≤0.72 g/kg/h. It is interesting to note that the rate of absorption from the intestinal tract in human subjects is slow, 0.2-

---

<sup>5</sup> Sestoft L. An evaluation of biochemical aspects of intravenous fructose, sorbitol and xylitol administration in man. *Acta Anaesthesiologica Scandinavica. Supplementum*. 82: 19-29 (1985).

<sup>6</sup> Sestoft L. An evaluation of biochemical aspects of intravenous fructose, sorbitol and xylitol administration in man. *Acta Anaesthesiologica Scandinavica. Supplementum*. 82: 19-29 (1985).

<sup>7</sup> FASEB, Health aspects of sugar alcohols and lactose, September 1986.

<sup>8</sup> JECFA, Summary Of Toxicological Data Of Certain Food Additives And Contaminants. WHO Food Additives Series NO. 13 WHO Technical Report Series No. 631 (1978); JECFA, Summary Of Toxicological Data Of Certain Food Additives And Contaminants. WHO Food Additives Series NO. 18 WHO Technical Report Series No. 569 (1983).

<sup>9</sup> Assumed to be 50%.

0.4 g/kg/h<sup>10</sup> (that is, below the xylitol elimination rate). In a limited clinical study,<sup>11</sup> an infusion rate of 0.125 g/kg/h was applied without side effects (higher infusion rates  $\geq 0.25$  g/kg/h resulted in adverse effects). Therefore, the infusion rate of xylitol from Addaven should be kept as low as possible, ideally  $< 0.1$  g/kg/h. A maximum recommended infusion rate has not been proposed in the draft Product information document. Given the maximum dose of xylitol from Addaven is 3 g/day or 0.06 g/kg/day for a 50 kg individual, it would be recommended that this be infused in no less than 1 h, to reduce the risk of liver damage and other adverse effects.

There was no evidence of oxalate deposits in the kidneys or any other non hepatic tissues in the short term repeat dose toxicity studies in mice, rats or rabbits when xylitol was administered by IV infusion. However, oxalate-rich calculi (which also contained calcium and phosphate) were observed in the urinary bladder of male mice in a 2 year oral carcinogenicity study (at  $\geq 15$  g/kg/day PO;  $\sim 11$  times the clinical dose on a g/m<sup>2</sup> basis and accounting for oral bioavailability).<sup>12</sup> Furthermore, oxalate was detected in the urine of rats that received a continuous daily 1 g/kg/h xylitol IV infusion for 5 days. This was not seen when glucose was infused. The extent of oxalate excretion increased  $\sim 4$ -5 times when rats were fed a vitamin B6 deficient diet. Studies using radiolabelled xylitol confirmed oxalate was produced from xylitol. A similar study in mice receiving dietary xylitol revealed an increase in oxalate excretion in vitamin B6 deficient animals (reviewed in JECFA, 1983).<sup>13</sup> An experiment performed in rabbits failed to show an effect of vitamin B6 deficiency on oxalate production; however, the vitamin B6 deficiency was only transient (compared with a more sustained deficiency in rats and mice) and, as indicated in the pharmacokinetics section, rats are a better model for oxalate production than rabbits. Therefore, the data from rabbits in regard to this endpoint should be considered of low relevance to human subjects. Vitamin B6 is an essential cofactor for the glycogen phosphorylase reaction, which is involved in the major metabolic pathway for xylitol. The increase in oxalate production when there is a deficiency in vitamin B6 may suggest that more xylitol is being metabolised by the generally minor metabolic pathway to oxalate. There may be a requirement to monitor vitamin B6 levels in patients receiving Addaven to minimise the risk of cerebrorenal oxalosis.

In summary, the daily IV dose of xylitol does not raise obvious safety concerns, provided one ampoule is infused over at least a 1 h period and vitamin B6 levels are maintained.

### Genotoxicity

Xylitol was reported to be not genotoxic in a standard battery of studies.<sup>14</sup> Negative results were returned in a bacterial mutagenicity assay with *S. typhimurium* (strains TA98, TA100, TA1535, TA1537 and TA1538), a mouse micronucleus test and an in vitro clastogenicity assay.

---

<sup>10</sup> The oral absorption rate of xylitol was reported as 10-20 g/h in human subjects. Based on a 50 kg individual, the absorption rate would be 0.2-0.4 g/kg/h: Grenby TH. *Advances in Sweeteners*. Chapman & Hall, London (1996).

<sup>11</sup> Matzkies F. Studies on the pharmacokinetics of carbohydrates as a basis for their use in parenteral nutrition. *Z. Ernährungswiss* 14: 184-216 (1975).

<sup>12</sup> Assuming an oral bioavailability of 50% and using g/kg to g/m<sup>2</sup> conversion factors of 3 and 33 for mice and humans (50 kg), respectively.

<sup>13</sup> JECFA, Summary Of Toxicological Data Of Certain Food Additives And Contaminants. WHO Food Additives Series NO. 18 WHO Technical Report Series No. 569 (1983).

<sup>14</sup> JECFA, Summary Of Toxicological Data Of Certain Food Additives And Contaminants. WHO Food Additives Series NO. 13 WHO Technical Report Series No. 631 (1978); FASEB, Health aspects of sugar alcohols and lactose, September 1986.

## Carcinogenicity

Two year oral carcinogenicity studies with xylitol were conducted in mice and rats. Based on the information available, the studies appear to have been adequately conducted. Provided the xylitol exposure resulting from the proposed dose and infusion rate of Addaven is below those expected with oral use of xylitol, the data with orally-administered xylitol are considered relevant for the current product.

There was an increased incidence of epithelial hyperplasia, squamous metaplasia and tumours (benign and malignant) in the urinary bladder of male mice that received  $\geq 15$  g/kg/day xylitol in the diet. There was a positive dose related correlation between bladder lesions and calculi, suggesting a possible link.<sup>15</sup> The NOEL for carcinogenicity was 3.1 g/kg/day PO in male mice and 31 g/kg/day PO in female mice. The doses are estimated to be 2 and 23 times in males and females, respectively, the clinical dose on a g/m<sup>2</sup> basis, taking into account the extent of oral bioavailability.<sup>16</sup> As the bladder tumours in mice appear to result from oxalate deposits (though the extent of calcium excretion is also a contributing factor), provided oxalate production is minimised (by using a low infusion rate and ensuring adequate vitamin B6 levels in patients), the bladder tumours are not considered a risk in patients receiving Addaven.

An increased incidence of adrenal medullary hyperplasia was observed in male and female rats treated with  $\geq 5$  g/kg/day and  $\geq 2.5$  g/kg/day, respectively, xylitol in the diet for 2 years, and an increased incidence of pheochromocytoma was observed in male (but not female) rats at dietary levels of 10 g/kg/day. The NOEL for preneoplastic lesions was 2.5 g/kg/day PO in males and 1 g/kg/day PO in females, which are estimated to be 4 and 1.5 times, respectively, the clinical dose on a body surface area basis, when taking into account the extent of oral absorption. No proliferative lesions have been observed in the adrenal glands of other species (mice, dogs) given xylitol supplementation in the diet.<sup>17</sup> Preneoplastic/neoplastic lesions in the adrenal glands have been observed in dietary studies in rats (but not other animal species) with other sugars (sorbitol, mannitol, lactitol, lactose).<sup>18</sup> An increase in these dietary sugars has been shown to increase intestinal calcium absorption<sup>19</sup> which in turn increases chromaffin cell proliferation leading to hyperplastic and neoplastic lesions in the adrenal gland.<sup>20</sup> Rats appear to be particularly sensitive to perturbations in calcium homeostasis. Given that these adrenal gland changes are likely secondary to ingestion of xylitol, a route of administration not relevant to the current product, and no proliferative lesions were observed in the adrenal gland of other species receiving xylitol, they are not considered a concern for patients receiving Addaven.

## Reproductive toxicity

No studies assessing the reproductive effects of xylitol were submitted. A published review<sup>21</sup> reported findings from a three generation study in rats and embryofoetal

<sup>15</sup> FASEB, Health aspects of sugar alcohols and lactose, September 1986.

<sup>16</sup> Assuming an oral bioavailability of 50% and using g/kg to g/m<sup>2</sup> conversion factors of 3, 6 and 33 for mice, rats and humans (50 kg), respectively.

<sup>17</sup> JECFA, Summary Of Toxicological Data Of Certain Food Additives And Contaminants. WHO Food Additives Series NO. 13 WHO Technical Report Series No. 631 (1978); FASEB, Health aspects of sugar alcohols and lactose, September 1986.

<sup>18</sup> FASEB, Health aspects of sugar alcohols and lactose, September 1986; Roe FJ, Bar A. Enzootic and epizootic adrenal medullary proliferative disease of rats: influence of dietary factors which affect calcium absorption. *Hum. Toxicol.* 4: 27-52 (1985).

<sup>19</sup> Brommage R, et al. Intestinal calcium absorption in rats is stimulated by dietary lactulose and other resistant sugars. *J. Nutr.* 123: 2186-2194 (1993).

<sup>20</sup> Tischler AS, et al. Vitamin D3, lactose and xylitol stimulate chromaffin cell proliferation in the rat adrenal medulla. *Toxicol. Appl. Pharmacol.* 140: 115-123 (1996).

<sup>21</sup> JECFA, Summary Of Toxicological Data Of Certain Food Additives And Contaminants. WHO Food Additives Series NO. 13 WHO Technical Report Series No. 631 (1978).

development studies in rats and rabbits. Fertility was unaffected in rats fed diets containing  $\leq 20\%$  xylitol (in a three generation study when both males and females were treated, and in an embryofetal development study when only females were treated). No adverse effects on embryofetal development were observed when rats and rabbits were exposed to xylitol via the diet (at  $\leq 20\%$ ) during the period of organogenesis. Estimated oral doses were  $\leq 20$  g/kg/day in rats and  $\leq 6$  g/kg/day in rabbits.<sup>22</sup> Assuming an oral bioavailability of 50%, these systemic doses are 30 and 18 times in rats and rabbits, respectively, the clinical dose of xylitol from Addaven on a body surface area basis.<sup>23</sup> Overall, no adverse effects on reproductive potential or embryofetal development are predicted with the proposed use of Addaven.

### ***Pregnancy classification***

The sponsor has not proposed a Pregnancy Category. This is considered acceptable as products of this type are exempted from pregnancy classification.

### ***Local tolerance***

Addaven will not be administered undiluted; one 10 mL ampoule of Addaven is required to be diluted in a glucose solution (100-1000 mL) or a sodium chloride solution (50-500 mL). The concentration of xylitol in diluted solutions would range from 3-27 mg/mL in glucose solutions and 6-50 mg/mL in sodium chloride solutions. In vitro, a xylitol concentration of 8.5 mg/mL in a salt solution did not lead to any appreciable haemolysis in blood from rats or humans. Therefore, the more dilute solutions (in 500-1000 mL) are unlikely to have any appreciable haemolytic effect. When xylitol (at 50 mg/mL) was applied to human blood in the presence of an oil/lecithin solution, no appreciable haemolysis was observed. It is unclear whether the presence of the oil/lecithin solution augments any haemolytic activity of xylitol, making the findings difficult to extrapolate to the proposed clinical use of Addaven. Therefore, the available in vitro data on haemolytic potential support the use of Addaven diluted in 500-1000 mL solutions but are not adequate to support the use in solution volumes  $< 500$  mL.

The pH of undiluted Addaven is stated to be 2.5 (draft PI document). A pH for the diluted solution(s) has not been provided. If the pH was still low after dilution, this may result in adverse injection site reactions. No adequate data were submitted to address this issue.

There may be sufficient clinical data with Addaven to address the outstanding injection site and haemolysis issues described above.

### ***Paediatric use***

Addaven is not proposed for use in children under the age of 12 years. No specific studies in juvenile animals were submitted.

## **Nonclinical summary and conclusions**

### **Summary**

- Fresenius Kabi Australia Pty Ltd has applied to register a new fixed dose combination product, Addaven, containing trace elements, with xylitol as an excipient. Addaven is

---

<sup>22</sup>  $20\% = 200\,000$  ppm; the ppm to mg/kg conversion factors for rats and rabbits are 10 and 33, respectively (divide ppm by conversion factor): Derelanko MJ. Toxicologist's Pocket Handbook. CRC Press Inc, Florida, USA (2000); Nielsen E, et al. Toxicological risk assessment of chemicals: A practical guide. CRC Press Inc, Florida, USA (2008).

<sup>23</sup> Using g/kg to  $\text{g}/\text{m}^2$  conversion factors of 6, 12 and 33 for rats, rabbits and humans, respectively (assuming a 50 kg patient).

proposed to be used to meet basal to moderately increased requirements of trace elements in parenteral nutrition. The proposed daily dosage of Addaven in adult patients with basal to moderately increased requirements is 10 mL (one ampoule).

- The overall quality of the submission (which consisted largely of published papers) was acceptable for the nature of this product (most components with a long history of clinical use). The proposed daily doses of the trace element components of Addaven are acceptable from a toxicological perspective. This evaluation focussed on xylitol, considered to be a new excipient for this route of administration.
- No primary or safety pharmacology studies with xylitol were submitted, which is considered acceptable. The secondary pharmacology studies raised no safety concerns with this excipient.
- Xylitol is predominantly metabolised in the liver, with a small amount of metabolism in the kidney. There are two notable metabolic pathways, one that leads to glycogen production and the other that leads to oxalate production.
- Toxicity studies with IV administered xylitol raised two major concerns: liver damage and oxalate production. There was no evidence of liver damage in animals when the infusion rate was similar to or below the xylitol elimination rate. Oxalate excretion was significant in rodents deficient in vitamin B6.
- Genotoxicity, carcinogenicity and reproductive toxicity studies with xylitol raise no relevant safety concerns for the proposed use of Addaven.
- There was no evidence of haemolysis of human blood with xylitol concentrations similar to that observed if Addaven is diluted in 500-1000 mL solutions. No comment can be made regarding haemolysis at higher concentrations (that is, if Addaven is diluted in solutions <500 mL). The pH of the diluted solution may also raise local tolerance concerns.

### Conclusions and recommendation

- The proposed doses of trace elements raise no obvious safety concerns.
- The proposed daily IV dose of xylitol does not raise obvious safety concerns, provided one ampoule is infused over at least a 1 h period. There may be a requirement to monitor and maintain vitamin B6 levels in patients. This will minimise the risk of adverse liver effects and cerebro-renal oxalosis in patients.
- There are no objections on nonclinical grounds to the proposed registration of Addaven.

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 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.

## Guidance

TGA has guidance on literature based submissions. A separate guidance no longer exists.

## 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)
- Periodic Safety Update Reports (PSURs)

## Paediatric data

The submission included a justification for no paediatric development program.

## Pharmacokinetics

### Studies providing pharmacokinetic data

The product was designed to have no pharmacodynamic effects besides maintaining or replenishing the nutritional status of the contained TE.

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

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.<sup>24</sup> Excretion of zinc is mainly in the faeces by transport through the intestinal mucosa, with a smaller amount in the bile and in urine.<sup>25</sup> 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, and hence are not under direct control.

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

### Evaluator's 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 TE 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 Parenteral Nutrition (PN).

## Pharmacodynamics

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

---

<sup>24</sup> Food and Nutrition Board 1997; Food and Nutrition Board 2000; Food and Nutrition Board 2001.

<sup>25</sup> Jeejeebhoy K. Zinc: an essential trace element for parenteral nutrition. *Gastroenterology* 137(5 Suppl): S7-S12 (2009).



## Dosage selection for the pivotal studies

Not applicable.

## Efficacy

### Evaluator's conclusions on efficacy

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 and close monitoring of blood levels. Otherwise there is support for the inclusion of the other elements which 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 Mn<sup>2+</sup> where the ESPEN guidelines recommends a higher dose which raises concerns regarding toxicity. The inclusion of some of the trace elements is not supported by the ASPEN guidelines based on perceived inadequate evidence.

**Table 2: 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  |
|---|-----------------|-------|---|--|---------------------|--|---|
|   | mmol            | mg    |   |  |                     |  |   |
| Cr <sup>3+</sup>                                      | 0.2             | 0.01  | 0.010-0.015mg/d <sup>a,g</sup>                            | Balance studies<br>Autopsies                 | Yes<br>Responds     | Carbohydrate and lipid metabolism affected, neuropathy   | None reported with chromium chloride <sup>b</sup>   |
| Cu <sup>2+</sup>                                      | 6.0             | 0.38  | 0.3-0.5mg/d <sup>a,g</sup>                                | Balance studies<br>Autopsies                 | Yes<br>Responds     | Hypochromic anaemia, neutropenia or pancytopenia   | None reported <sup>b</sup><br>Possible liver damage concern   |
| Fe <sup>3+</sup>                                      | 20              | 1.10  | 1.1mg/d <sup>a,c</sup><br>1-1.2mg/d <sup>f</sup>          | Balance & tolerance studies<br>Autopsies     | Yes<br>Responds     | iron deficiency anaemia  | Possible infection risk <sup>d</sup>  |
| Mn <sup>2+</sup>                                      | 1               | 0.055 | 0.055mg/d <sup>a,c</sup><br>0.2-0.3mg/d <sup>f</sup>      | Balance studies<br>Autopsies                 | Yes x 1<br>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 <sup>-</sup>  | 1               | 0.13  | 0.13mg/d <sup>a,c</sup><br>0.1mg/d <sup>f</sup>           | Based on oral balance and absorption studies | Not reported        | Described clinically otherwise   | None reported<br>Both hyperthyroidism and hypothyroidism described clinically                                       |
| F <sup>-</sup>  | 50              | 0.95  | 1mg/d <sup>a,g</sup>                                      | No supporting data                           | Not reported        | Described clinically otherwise   | None reported<br>Described clinically   |
| MoO <sub>4</sub> <sup>2-</sup> (as Mo <sup>6+</sup> ) | 0.2             | 0.019 | 0.02mg/d <sup>a,c</sup><br>0.019mg/d <sup>f</sup>         | Balance studies<br>Limited data              | Yes x 1<br>Responds | Progressive tachycardia, tachypnoea, neurological and visual changes, and eventually coma; reduced activity of sulphite oxidase and xanthine oxidase   | None reported   |
| SeO <sub>3</sub> <sup>2-</sup> (as Se <sup>4+</sup> ) | 1               | 0.08  | 0.06-0.1mg/d <sup>a,c</sup><br>0.02-0.06mg/d <sup>f</sup> | Balance studies<br>Autopsies                 | Yes<br>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 <sup>2+</sup>                                      | 77              | 5.0   | 2.5-5mg/d <sup>a,g</sup><br>3.2-6.5mg/d <sup>f</sup>      | Balance studies<br>Autopsies                 | Yes<br>Responds     | eczematous rash, nail changes, appecia, mental apathy and depression, visual dysfunction, and impaired immune function   | Few cases hypotension, pulmonary oedema, diarrhoea, vomiting, jaundice, and oliguria                                |

<sup>a</sup> ASPEN recommended

<sup>b</sup> Despite raised serum and tissue levels in some patients

<sup>c</sup> AuSPEN recommended

<sup>d</sup> Postulated related to saturation of transferrin

<sup>e</sup> ASPEN, not routinely added in US

<sup>f</sup> AuSPEN no recommended dose

<sup>g</sup> ESPEN recommended

## Safety

### Post marketing data

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.

### **Evaluator's conclusions on 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.

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 IV xylitol was prohibited on the advice of Australian Drug Evaluation Committee (ADEC). It has been accessed under the Special Access Scheme (SAS). The sponsor has chosen to submit the evidence for it in the nonclinical section.<sup>26</sup>

*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.)<sup>27,28</sup>*

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

### **First round benefit-risk assessment**

#### **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).

#### ***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.

---

<sup>26</sup> 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 and are included in the nonclinical modules, since they do not relate to clinical use of Addaven and therefore do not fit into the clinical sections of the dossier.

<sup>27</sup> Conyers RA, et al. The metabolic production of oxalate from xylitol. *Int J Vitam Nutr Res Suppl.* 28: 9-28 (1985).

<sup>28</sup> Xylitol - Prohibited Imports - Nonclinical Safety Assessment, 24 November 2011.

### ***Correction of mild deficiency states***

The problem is to define a mild deficiency state. A marked deficiency is usually clearly evident and requires additional trace elements. Mild deficiency is more likely to be suspected based on history, particularly as plasma levels often do not reflect body stores.

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

The exception is fluoride, included 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:

*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.*

### **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.

### **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.*

### **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.

**Clinical questions**

Not applicable.

**V. Pharmacovigilance findings****Risk management plan**

The sponsor submitted a EU Risk Management Plan (RMP) version 6.0 (dated 17 March 2015, DLP 31 July 2014), with an Australian Specific Annex (ASA) (undated), which was reviewed by the RMP evaluator.

**Safety specification**

The sponsor provided a summary of ongoing safety concerns which are shown at Table 3.

**Table 3: Ongoing safety concerns.**

| Ongoing safety concerns           |   |
|-----------------------------------|---|
| <b>Important identified risks</b> | <p>Hypersensitivity to the active substances or to one of the excipients</p> <p>Accumulation of trace elements in patients with impaired biliary and/or renal function</p> <p>Accumulation of trace elements in patient with biochemical or clinical evidence of liver dysfunction (especially cholestasis)</p> <p>Accumulation of copper in Wilson's disease</p> <p>Accumulation of manganese in the presence of cholestasis</p> <p>Haemosiderosis in case of chronic overload of iron</p> |
| <b>Important potential risks</b>  | None  |
| <b>Missing information</b>        | <p>Posology for children &lt;15kg</p> <p>Use in pregnant women</p>  |

***RMP reviewer comments***

Subject to the evaluation of the nonclinical and clinical aspects of the Safety Specification, it is recommended that:

*The RMP should consider risks associated with the intravenous administration of the excipient, xylitol and include relevant safety concerns as appropriate.*

**Pharmacovigilance plan*****Proposed pharmacovigilance activities***

Routine pharmacovigilance activities are proposed for all safety concerns in the EU RMP and the ASA. No additional pharmacovigilance activities are proposed.

***RMP reviewer comments***

Routine pharmacovigilance, given the proposed use, is considered to be acceptable. For any safety concerns included as a result of the recommendation (or recommendations from the clinical and nonclinical evaluators) a pharmacovigilance plan should be included for each. Any subsequent revision to the RMP/ASA will be evaluated.

**Risk minimisation activities*****Sponsor's conclusion in regard to the need for risk minimisation activities***

The sponsor has concluded that only routine risk minimisation activities are required to mitigate the risks associated with Addaven. No additional risk minimisation activities are proposed.

***RMP reviewer comments***

Addaven will typically be used in a highly specialised environment with clinical review and monitoring. Routine risk minimisation is acceptable as long as the risk minimisation recommendations are satisfactorily responded to.

**Reconciliation of issues outlined in the RMP report**

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

***Recommendation #1 in RMP evaluation report***

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports, respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

***Sponsor response***

Nonclinical safety specification was added to the RMP.

***Evaluator's comment***

The sponsor's addition to the nonclinical safety specification, including information on the xylitol excipient is noted. Acceptability of this information may be subject to consideration by the nonclinical evaluator.

***Recommendation #2 in RMP evaluation report***

Addaven is to be given as a diluted IV infusion. The "Dosage and Administration" should include recommended infusion rates to minimise the risk of administration error.

***Sponsor response***

The following underlined text has been added to the PI under the "Method of Administration" Heading:

*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.*

The RMP has been revised accordingly.

***Evaluator's comment***

This is acceptable from an RMP perspective. PI changes are subject to final determination by the Delegate.

***Recommendation #3 in RMP evaluation report***

The sponsor should also confirm whether a particular infusion site is recommended (for example, peripheral versus central venous access). If so, such information should be included in the PI.

***Sponsor response***

The following underlined text has been added to the PI under the "Method of Administration" Heading:

*Addaven must not be given undiluted. Addaven shall be diluted in a parenteral nutrition solution/emulsion before given as an intravenous infusion via central or peripheral venous access. Peripheral administration should always consider osmolarity of the admixture.*

The RMP has been revised accordingly.

***Evaluator's comment***

This is acceptable from an RMP perspective. PI changes are subject to final determination by the Delegate.

***Recommendation #4 in RMP evaluation report***

The RMP should consider risks associated with the intravenous administration of the excipient, xylitol and include relevant safety concerns as appropriate.

***Sponsor response***

Fresenius Kabi does not understand the reason behind adding such a cautionary statement to the PI in order to maintain B6 levels to minimize the risk of oxalosis.

Fresenius Kabi seeks confirmation from the clinical evaluator that adding such a cautionary statement is really necessary.

***Evaluator's comment***

It appears that the sponsor has not directly responded to this recommendation but rather mistakenly repeated a response for the clinical evaluation report.

Should the Delegate consider that safety issues arise from the IV administration of the xylitol excipient then the RMP documentation may need to be revisited.

It is noted that the nonclinical evaluator has provided advice on this issue.

***Recommendation #5 in RMP evaluation report***

For any safety concerns included as a result of the recommendation (or recommendations from the clinical and nonclinical evaluators) a pharmacovigilance plan should be included for each. Any subsequent revision to the RMP/ASA will be evaluated.

***Sponsor response***

No new safety concerns were identified; therefore, no new pharmacovigilance plan was included.

***Evaluator's comment***

No specific safety concerns regarding xylitol have been included in the revised versions of the RMP.

**Summary of recommendations*****Outstanding issues******Issues in relation to the RMP*****Issues for the delegate's consideration**

The sponsor's addition to the nonclinical safety specification, including information on the xylitol excipient is noted. Acceptability of this information may be subject to consideration by the nonclinical evaluator.

It appears that the sponsor has not directly responded to RMP evaluation report but rather has mistakenly repeated a response for the clinical evaluation report. Should the Delegate consider that safety issues arise from the IV administration of the xylitol excipient then the RMP documentation may need to be revisited.

**Issues for the sponsor's action**

The sponsor has included a table detailing the routine risk minimisation activities proposed for Australia but has not compared with those proposed in the EU. Such a table, as per TGA ASA guidance, should be included when the document is next updated.

The ASA should be amended with a date and version number to accommodate future updates.

***Advice from the Advisory Committee on the Safety of Medicines (ACSOM)***

ACSOM advice was not sought for this submission.

***Comments on the safety specification of the RMP******Clinical evaluation report***

The Safety Specification in the draft RMP is satisfactory.

***Nonclinical evaluation report***

The nonclinical Safety Specification in the RMP does not discuss any potential risks with xylitol. The TE Solution (4204) discussed in this section is not Addaven and does not contain xylitol. Therefore, data from studies conducted with TE Solution 4204 do not address safety concerns associated with xylitol. The nonclinical Safety Specification requires major revision to include potential risks associated with xylitol.

**RMP evaluator comment**

It is noted that information regarding xylitol has now been included in the nonclinical safety specification of the updated RMP documentation. Acceptability of this information may be subject to consideration by the nonclinical evaluator.

***Key changes to the updated RMP***

EU RMP version 6.0 (dated 17 March 2015, DLP 31 July 2014) with an ASA has been superseded by:

- EU RMP Version 7.0 (dated 23 February 2016, DLP 31 July 2014) with an ASA (undated, submitted on 24 February 2016)



**Table 4: Summary of key changes between EU RMP v 6.0 and EU RMP v 7.0.**

| Summary of key changes between EU RMP v 6.0 and EU RMP v 7.0 |  |
|--|--|
| Safety specification   | Missing information item “Posology for children <15kg” has been amended to “Posology for children under 12 years of age” |
| Pharmacovigilance activities                                 | Nil significant change - routine pharmacovigilance only proposed.  |
| Risk minimisation activities                                 | Nil significant change - routine risk minimisation only proposed.  |
| ASA  | Changes made in response to RMP evaluation report (see section 5 below).   |

*RMP evaluator comment*

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented (see below).

***Suggested wording for conditions of registration****RMP*

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

- Implement EU RMP Version 7.0 (dated 23 February 2016, DLP 31 July 2014) with an ASA (undated, submitted on 24 February 2016) and any future updates as agreed with the TGA.

**VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate’s overview and recommendations:

**Risk-benefit analysis****Delegate’s considerations**

This submission to register Addaven is deemed approvable by quality (pharmaceutical chemistry/biocompatibility), nonclinical (toxicology), and RMP evaluators. Addaven essentially contains an admixture of nine trace elements (chromic, cupric, ferric, manganese, potassium, fluoride, molybdate, selenium and zinc) as active ingredients. Its proposed indication is to “meet basal to moderately increased requirements of trace elements in parenteral nutrition.” As mooted by the clinical evaluator and in line with the indication for most of the other registered parenteral products in Australia and, to emphasize the fact that most of the trace elements are indeed available in everyday diet, it is suggested that the indication be modified to:

*meet basal to moderately increased requirements of trace elements in parenteral nutrition in adults, when either oral or enteral nutrition is inappropriate (preferred option to that of the clinical evaluator).*

Addaven is a reformulation of Addamel N which has been approved in Europe for decades, and which is being supplied in Australia under Special Access Scheme since 2001. Although Addamel N failed to gain registration approval in Australia due to technical issues, it remained on the ARTG export only list from 30 June 2009 to 04 August 2015 followed by cancellation. Addaven is registered nationwide in Europe (including UK), NZ and Switzerland. There is no application in USA or Canada.

The clinical evaluator is not recommending authorisation stating that:

- It (the submission) fails to meet some of the requirements of a LBS

The Delegate believes that the submission appropriately meets the requirements of LBS because:

- Even viewing Addaven as a new chemical entity (NCE) in Australia, its ‘protégé’ Addamel N has been registered in Europe for many years. Moreover, Addaven itself has been registered in Europe, NZ and Switzerland for some time now;
- Even if the marketing of Addaven elsewhere is less than 10 years, the LBS for Addaven application appeared appropriate given that a previous submission of Addamel N ( a protégé of Addaven) claimed orphan status;
- While there are individual (single) trace element parenteral formulations/preparations on the Australian market, the Delegate believes that there is *no admixture parenteral composition or combination of trace elements* as such on the Australian market. Addaven will clearly fill the latter area of unmet clinical need as a ready to use parenteral trace elements combination. It will also save time and reduce probable errors from assembling those trace elements separately for each individual patient’s use, each time the requirement arises;
- The sponsor’s argument that Addaven is a new formulation of a pre-existing preparation Addamel N (and thereby inferring that LBS is appropriate) is acceptable.
- There exists an ADEC recommendation to prohibit the use of one of the excipient components: Xylitol.

The Delegate believes that the above is no longer current for the following reasons:

- The above statement on ADEC recommendation refers to Resolution 303 around 1972. Amendment to Customs Regulations (13 July 2013) stated

*These substances (Xylitol and preparations containing xylitol under Schedule 8) do not have a potential safety risk unless consumed at high dose.*

The latter has led to the removal of Schedule 8 labelling of Xylitol and Xylitol containing preparations and to the **overturning of the ADEC recommendation on the banning importation placed on Xylitol and Xylitol containing preparations.** The amendment to Customs Regulations was based on the 2011 toxicology review conducted on behalf of Customs. The toxicology review stated:

- The following adverse events were reported in subjects treated with xylitol alone or in combination with other sugars by IV infusion: cerebro-renal oxalosis, acute renal failure, increases in plasma/blood concentration and urinary excretion of uridine, purine and lactic acid, decreases in plasma/blood concentrations of inorganic phosphate and pyruvic acid, and rare cases of deaths.

- Based on the review of the safety profile and the current uses of xylitol, xylitol may be safely used in oral and topical therapeutic products. Xylitol is already permitted as a food additive and for use in oral and topical therapeutic products in Australia. The use of xylitol in parenteral therapeutic products is subject to the assessment of safety, efficacy (if it is intended to be an active ingredient) and quality by the TGA.

In addition to the above:

- It is stated in the current toxicology evaluation report for this submission that “there are no objections on nonclinical grounds to the proposed registration of Addaven”;
- Xylitol is an excipient in some registered prescription drugs (MS Contin, Abilify, Nicotinell gum), in several over-the-counter (OTC) remedies (Blackmores, Brocca, Gavison) and probably in some food products;
- The CE stated that the proposed dose and rate of administration of Xylitol appears to be well below that causing toxicity. The clinical evaluator also referred to the absence of pharmacokinetic data. In that regard, the quality evaluator stated that no bioavailability data are required as the product, after dilution, is a simple aqueous solution that is given by intravenous infusion in an admixture with emulsions of amino acids, lipids and glucose used for TPN.

It is to be stated that there are no standard clinical trials in the LBS to register Addaven. The Delegate believes that the latter is not to be unexpected given, the probability of multiple trace elements deficiencies in those patients whose sickness or condition are deemed serious enough to be placed on parenteral nutrition. It will be difficult or near impossible to conduct well designed clinical trials elucidating the deficiency and replacement outcome of each individual trace element in those very sick patients. The expected or supposed efficacy of Addaven is essentially therefore based on physiological and anecdotal inferential evidence from the literature submitted. The evidence alluded to the physiological purposes and the functional requirements of each trace element in Addaven. In particular, the pathological consequences of a trace element being deficient and the subsequent efficacy outcome of its being replaced were discussed.

The Delegate considers that there are no major concerns in terms of safety. Issues concerning the possible toxicity of any of the trace elements in Addaven during TPN [from such things as over dosage, organ (liver, kidney) dysfunction] will be minimised by the fact, that treatment management of patients and the TPN use of Addaven will most likely occur in tertiary hospitals under intense monitoring. The safety aspects of Xylitol have been previously addressed above.

The clinical evaluator assessed the benefit-risk balance of Addaven as unfavourable based on the usual process of assessment. The clinical evaluator however commented

*it may be that different criteria are needed in this case.*

The clinical evaluator’s unfavourability has to do with (a) paucity of recent, well designed research studies/trials, especially in *Australia/NZ and environs*, on the provision of trace elements in parenteral nutrition and (b) uncertainty as to the adequacy and nontoxicity of Addamel N which was referred to in the LBS. Considering the above, the Delegate is of the opinion that the benefit-risk balance of Addaven is favourable for the following reasons:

- The fact that human physiology is relatively constant over generations demands little or no new changes in parenteral nutrition practice requirements;
- Australia is a diverse population and outcomes of parenteral nutrition studies outside of Australia can be fully applied to the Australia’s population;
- For ethical or logistical reasons, high level evidence as in randomised controlled studies are not always possible in the area of parenteral nutrition;

- The fact that Addamel N has been registered and used in Europe for many years attest to its parenteral nutrition adequacy and nontoxicity.

The draft PI required modifications as raised in the evaluation reports before finalisation of the application.

### **Proposed action**

Based on my analysis of the evidence from the submitted data evaluation, the Delegate believes at this stage that the Addaven application is approvable. The latter is subject to resolving all issues which may arise from the ACPM deliberations and finalisation of matters pertaining to the draft PI and RMP to the satisfaction of the TGA.

### **Request for ACPM advice**

The committee is requested to provide advice on the following specific issues:

- Approvability of the Addaven application based on the Delegate's rational discussion
- Acceptability of the Delegate's proposed modified indication
- Advice on any other issues relevant to a decision on whether or not to approve this application.

### **Response from sponsor**

#### ***Delegate's discussion - INDICATIONS - Page 39 request for ACPM advice***

As mooted by the clinical evaluator and in line with the indication for most of the other registered parenteral products in Australia and, to emphasise the fact that most of the trace elements are indeed available in everyday diet, it is suggested that the indication be modified to:

*meet basal to moderately increased requirements of trace elements in parenteral nutrition in adults, when either oral or enteral nutrition is inappropriate (preferred option to that of the clinical evaluator).*

#### *Response*

We thank the TGA Delegate and appreciate the modification of the indication. We confirm the proposed indication is acceptable to the company.

#### ***Following evaluation (Round 2) of the Section 31 response the following text has been recommended by the TGA***

The following (underlined) alternative statement is recommended under '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. The baby may be at risk of zinc induced copper deficiency. However, the amount of zinc in the milk may not be sufficient to induce copper deficiency in infants. Therefore, the potential hazards of zinc to the infant must be weighed against the potential benefits to the mother before Addaven is administered to mothers who are breast feeding."

#### *Response*

We acknowledge the need for consistent product information for parenteral nutrition products and we are aware that for SmofKabiven (FK product) and other products containing zinc, the theoretical risk of zinc induced copper deficiency is included in the Australian PI. However, please note that Addaven also includes copper as an active ingredient (which is not the case for other zinc preparations). Therefore, we feel it is unreasonable to include a warning for zinc induced copper deficiency in the PI of Addaven.

In fact, the risk of copper deficiency in the baby would be higher if the mother is on PN, and **does not** take Addaven. Please refer to our previously submitted responses. We would like the TGA to consider the below mentioned text (which is included in the PI for Kabiven), however we will accept the final decision of the TGA Delegate:

*'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. The prescriber should consider the benefit/risk relationship before administering Addaven to breastfeeding women.'*

**Item 9 - Page 32 request for ACPM advice**

The nonclinical evaluator also expressed concern that:

*The increase in oxalate production when there is a deficiency in vitamin B6 may suggest that more xylitol is being metabolised by the generally minor metabolic pathway to oxalate. There may be a requirement to monitor vitamin B6 levels in patients receiving Addaven to minimise the risk of cerebro-renal oxalosis. Given the concerns of ADEC in relation to xylitol toxicity it is recommended that a warning be inserted in relation to this either under Precautions or Interactions with Other Medicines. It has been recommended the following text be inserted: 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.*

**Response**

Human intravenous administration of xylitol can produce metabolic acidosis, and a syndrome of effects including diuresis, oligouria, azotemia, acidosis, hepatic disturbances and hyperuricaemia, as well as renal and cerebral toxicity related to deposition of oxalate crystals in the brain, kidney and other organs. Deaths or serious adverse events have been reported with doses of  $\geq 150$  g xylitol per day (approximately 50 times the dose of xylitol administered during recommended use of Addaven) for more than 4 days ( $\geq 2.5$  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 50 g/day (approximately 16 times the dose of xylitol administered during recommended use of Addaven) and at these doses the intravenous safety profile of xylitol has been shown to be similar to or better than that of an equivalent dose of glucose. In a few animal studies published approximately 40 years ago oxalate formation in vitamin B6 deficient rats has been shown. After high intravenous infusion of xylitol at doses of 24 g/kg/day for 5 days urinary excretions of oxalate were increased significantly. In these old studies oxaluria were detected at extremely high doses but no organ deposition was detected. Nevertheless, it was suggested that vitamin B6 deficiency may be a factor contributing to oxalate crystal deposition seen in some patients after infusion with xylitol at very high doses. However, this extrapolation from sporadic and old animal studies seems to be rather questionable and not really founded and justified by studies. Human data on oxalate deposits seem to be more related to extremely high Xylitol doses which were used in the past for nutrition and energy uptake but this would be less relevant for the low doses of Addamel.

We feel there is no basis for this warning and this statement need not be included in the Product Information.

**RMP (Second Round) - Outstanding issues - Page 33 Request for ACPM advice**

The following comments have been made:

*It appears that the sponsor has not directly responded to RMP evaluation report but rather has mistakenly repeated a response for the clinical evaluation report. Should*

*the Delegate consider that safety issues arise from the IV administration of the xylitol excipient, then the RMP documentation may need to be revisited.*

#### Response

We apologise for this oversight. The recommendation stated:

*The RMP should consider the risk associated with the intravenous administration of the excipient, xylitol and include safety concerns as appropriate.*

Please find our correct response below:

*Addaven contains xylitol (300 mg/mL) as a stabiliser. Xylitol has no clinical function in the product, and is included only as an excipient. The amount of xylitol administered per day as part of Addaven is 3 g per day (approximately 71 mg/kg body weight (bw)/d for a 42 kg child and 50 mg/kg bw/day for a 60 kg adult). Xylitol has been used as an excipient in oral products (in foods, confectionary, and registered therapeutic goods) in Australia for decades. It has also been used as an excipient in parenteral products for decades in the EU and many other countries. During the 1970s and into the 1980s there was extensive use of xylitol (particularly in Germany) as a source of energy in PN. Many reviews and studies report its use either as the sole energy source, or in combination with glucose and fructose. Xylitol has no clinical purpose in Addaven, but the amounts of xylitol administered as an energy source are greatly in excess of the exposure during Addaven administration, and studies in which xylitol has been used as an energy source in PN can provide information on the possible effects or otherwise of xylitol during use of Addaven. This has resulted in a significant amount of information on the safety or otherwise of xylitol administered via intravenous infusion. A number of clinical studies have been conducted in which xylitol has been administered as the sole carbohydrate source in PN, usually compared to glucose as the sole carbohydrate source, either in a control group of patients or in a crossover study design. Studies administering more than 100 g xylitol per day as part of PN for periods of up to 5 days found no adverse effects from xylitol administration, and little difference in clinical chemistry parameters compared to an equivalent dose of glucose except for improved blood glucose control. This has been found to be the case in diabetic patients as well as non diabetic patients. Other studies in which xylitol has been administered in combination with glucose and/or fructose have found no adverse effects after administration of 90-150 g or more of xylitol per day for periods of 2 to >10 days at administration rates of 0.125 g/kg bw/h or less. The effects of the carbohydrates administered in combination seem to be independent of each other, and the effects of xylitol are related to the dose of xylitol, and not the total carbohydrate dose. At the doses of up to 150 g/day, for use as sole energy source, significant toxicity concerns were described for xylitol. IV administration of xylitol can produce metabolic acidosis, and a syndrome of effects including diuresis, oligouria, azotemia, acidosis, hepatic disturbances and hyperuricaemia, as well as renal and cerebral toxicity related to deposition of oxalate crystals in the brain, kidney, and other organs. Deaths or serious adverse events have been reported with doses of  $\geq 150$ g xylitol per day (approximately 500 times the dose of xylitol administered during recommended use of Addaven) for more than 4 days ( $\geq 2.5$  g/kg body weight/day) with total doses generally in excess of 1 kg. Whereas no adverse effects have been reported at IV doses of xylitol up to 50 g/day (approximately 160 times the dose of xylitol administered during recommended use of Addaven) and at these doses the intravenous safety profile of xylitol has been shown to be similar to or better than that of an equivalent dose of glucose. Therefore, the daily dose of xylitol in Addaven of 3 g per day (approximately 71 mg/kg b.w. for a 42kg child and 50 mg/kg/day for a 60 kg adult is by far below the doses used for parenteral nutrition for energy and therefore without any risk.*

**Advisory Committee considerations**

The Advisory Committee on Prescription Medicines (ACPM) resolved to recommend to the TGA Delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Addaven concentrate for solution for infusion containing nine TE to have an overall positive benefit-risk profile for the delegate's amended indication:

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

In making this recommendation, the ACPM:

- advised that the proposed dose and rate of administration of xylitol appears to be well below that causing toxicity
- noted that there is significant post marketing experience with Addamel N and that no new risks were identified with Addaven
- was of the view that there is no major safety concern with the nine trace elements included in the product
- noted that the application meets the standards of a LBS
- advised that the appropriate age group for use of Addaven is in patients over 12 years of age and that the PI had been appropriately annotated.

***Proposed conditions of registration***

The ACPM agreed with the delegate on the proposed conditions of registration.

***Proposed PI/CMI amendments***

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

***Specific advice***

The ACPM advised the following in response to the delegate's specific questions on this submission:

- Approvability of the Addaven application based on the Delegate's rational discussion.

The ACPM advised that Addaven is approvable based on its positive benefit/risk ratio.

- Acceptability of the Delegate's proposed modified indication.

The ACPM advised that the Delegate's proposed modified indication was appropriate.

- Advice on any other issues relevant to a decision on whether or not to approve this application.

The ACPM had no objection against the approval of this application. There were no other issues.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

**Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Addaven concentrated injection ampoule, indicated for:

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

### **Specific conditions of registration applying to these goods**

- The Addaven (chromic chloride hexahydrate, Cupric chloride dehydrate, Ferric chloride hexahydrate, Manganese chloride tetrahydrate, Potassium iodide, Sodium fluoride, Sodium molybdate dihydrate, Sodium selenite and Zinc chloride) EU RMP Version 7.0 (dated 23 February 2016, DLP 31 July 2014) with an ASA (undated, submitted on 24 February 2016) and any future updates as agreed with the TGA included with the submission, will be implemented in Australia.

## **Attachment 1. Product Information**

The PI approved for Addaven at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **Attachment 2. Extract from the Clinical Evaluation Report**



## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

<https://www.tga.gov.au>