CBG MEB

Public Assessment Report

Scientific discussion

Supliven, concentrate for solution for infusion

(chromic chloride hexahydrate, copper chloride dihydrate, ferric chloride hexahydrate, manganese chloride tetrahydrate, potassium iodide, sodium fluoride, sodium molybdate dihydrate, sodium selenite anhydrous, zinc chloride)

NL License RVG: 113680

Date: 26 May 2015

This module reflects the scientific discussion for the approval of Supliven, concentrate for solution for infusion. The marketing authorisation was granted on 18 June 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Supliven, concentrate for solution for infusion from Fresenius Kabi Nederland BV.

The product is indicated in adults and children for the use in addition to parenteral nutrition to cover the need of trace elements if there is an immediate need or if it is expected that parenteral nutrition will be longer than 2 weeks.
A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a line extension to Addamel-N concentrate for solution for infusion (NL license RVG 12068), a well established medicinal product which has been registered since 10 July 1989. The changes compared to the existing product concern a change in name and a slight adjustment in the concentrations of several trace elements.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a bibliographic application.

II. QUALITY ASPECTS

II.1 Introduction

Supliven is an additive in intravenous nutrition and consists of a clear solution, colorless to slightly yellow and essentially free from particles. Osmolality is: ± 3100 mosm/kg H2O and pH is 2.5.

The product consist of 53.3 µg chromic chloride hexahydrate, 166 µg potassium iodide, 1.0 mg copper chloride dihydrate, 0.198 mg manganese chloride tetrahydrate, 2.1 mg sodium fluoride, 48.5 µg sodium molybdate dihydrate, 173 µg sodium selenite anhydrous, 5.4 mg ferric chloride hexahydrate, 10.5 mg zinc chloride.

The excipients are xylitol, hydrochloric acid and water for injections. Osmolality is: ± 3100 mosm/kg H2O and pH is 2.5.

The product is contained in a polypropylene ampoule (10 ml).

II.2 Drug Substances

The active substances are all inorganic substances which are well known and described in the European (Ph.Eur.). The MAH provided full details of each drug substance.

Manufacturing process
The MAH provided sufficient information on the manufacturing process of each of the active substances.

Quality control of drug substances
The drug substance specifications are in line with the Ph.Eur. or the USP with additional requirements for microbiological quality.
Potassium iodide has an additional test for residual solvents. The specifications are acceptable in view of the route of synthesis and the various European guidelines.

Stability of drug substances
Since all drug substances are inorganic substances which do not degrade, no stability data are necessary.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Supliven is an adapted version of the medicinal product Addamel-N. In comparison to Addamel-N, Supliven contains decreased concentrations of copper, manganese and zinc, and an increased concentration of selenium, according to current recommendations. No significant changes have been made to the pharmaceutical properties of the product, hence the product has the same physico-chemical 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. Compatibility studies, using Addamel-N as a reference, have confirmed that the difference in composition between the two products does not have any impact on the admixing properties of the products. Compatibility of the drug product with macronutrients amino acids, glucose and lipids, together with electrolytes and micronutrients (vitamins and trace elements) has been adequately discussed.
The pharmaceutical development of the product been adequately performed.

Manufacturing process
The manufacturing process consists of mixing of the solution, filtration of the solution, filling and sealing of the ampoules by Blow-Fill-Seal-system and steam sterilization.
The applicant provided validation information on the BFS machine, the mix-to-sterilization time, the sterilization step and the microbiological container integrity of the PP ampoules. The validation of those steps were already approved for Addamel-N and are considered to be acceptable for this application. Hence no further information is requested.
Full process validation on the first three commercial batches will be performed post approval.

Control of excipients
The excipients comply with the Ph.Eur.. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, pH, density, extractable volume, visible particles, subvisible particles, bacterial endotoxins and sterility. The release and shelf life limits are identical with the exception of density which is not included in the shelf life specification. The specifications are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three production-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided three production-scale batches stored at 25°C/60% RH (up to 9 months), 30°/75% RH (up to 9 months), 30°C/35% RH (up to 9 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging.
The physical, chemical and microbiological stability and the water loss results presented, together with the documented proof of stability of the pharmaceutically equal product Addamel-N is considered sufficient to grant the claimed shelf-life of 36 months without special storage condition.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Supliven has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
The following post-approval commitment was made:

- The MAH committed to perform full process validation on the first three commercial batches of the medicinal product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Supliven is a line extension which is expected to substitute an available product, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

The MAH has provided a non-clinical overview discussing pharmacology, pharmacokinetics and toxicology of all the constituents. Reference is made to governmental documents, such as from the European Food Safety Authority (EFSA) and WHO. The changes proposed in manganese chloride and zinc chloride are accepted, as both are less toxic constituents (class 4 as defined in ICH-Q3D-document), and no limit has been specified.
Although lower than in Addamel-N, the concentration of copper chloride is still 3 times higher than the limits proposed in the Q3D step 2 document. However, the limits provided in this guideline are below therapeutical intention. An adequate justification for the amount of copper in the Supliven formulation has been provided with reference to the tolerable upper intake levels for copper defined by the EU Scientific Committee for Food (SCF) and the US Food and Nutritional Board (FNB).
The company has used adequate references and arguments to support the use of selenite in the proposed enhanced concentration. Administration of one ampoule of Supliven results in 79 µg/day of the active ingredient selenite (as Se4+). This amount is below the proposed limits of the Q3D guideline for elemental impurities. The justification is sufficient and can be accepted.
Overall, the overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Trace elements are an essential part of any parenteral nutrition regimen to prevent ineffective utilization of macronutrients like energy substrates and aminoacids and prevent deficiency symptoms which are specific to each trace element. For almost 30 years it has been used in a formulation with the name Addamel-N and under different trade names as an additional supply to intravenous nutrition with the therapeutic indication to meet basal to moderately increased requirements in a fixed combination of the trace elements zinc, copper, iron, selenium, manganese, molybdenum, chromium, fluoride and iodide.

The combination has been based on the estimated amounts of trace elements that are normally absorbed from the oral diet and should have no other pharmacodynamics effects besides maintaining or repleting the nutritional status.

Through this line extension based on well established use the MAH applied for an updated version of Addamel-N in which the concentrations of copper, manganese and zinc are decreased and the concentration of selenium is increased. Herewith the name “Addamel-N” is changed to “Supliven”.
The MAH stated that the changes are minor and will not influence the physical properties of the product.

The concentrations of trace elements are adapted following the information based on an extensive overview of the literature up to 2012 and a combination of the last versions of the international Aspen (USA) and Espen (Europe) guidelines for parenteral nutrition.

The recommended standard dosage in patients with basal or moderately increased requirement is 10 ml (one ampoule) which has not been changed with the new formulation. For children weighing 15 kg or more the recommended dosage is 0.1 ml/kg bodyweight/day).

IV.1 Discussion on the new composition

The changed formulation of Supliven compared to the former formulation of Addamel-N is shown in the table below.

	Original Formulation (Addamel) in 10 ml		Current Formulation (Addamel N) in 10 ml		New Formulation in 10 ml	
	mg	µmol	mg	µmol	mg	µmol
Zinc	1.3	20	6.5	100	5.0	77
Copper	0.3	5	1.26	20	0.4	6.3
Selenium	-	-	0.03	0.4	0.08	1.0
Manganese	2.2	40	0.275	5.0	0.055	1.0
Chromium	-	-	0.01	0.2	0.01	0.2
Iron	2.7	50	1.1	20	1.1	20
Molybdenum	-	-	0.019	0.2	0.019	0.2
Iodide	0.13	1.0	0.13	1.0	0.13	1.0
Fluoride	0.95	50.0	0.95	50.0	0.95	50.0

All PN (parenteral nutrition) prescriptions should include a daily dose of a full range of trace elements. However the need for trace elements may be quite different in individual patients depending from the underlying disease. Prolonged home PN has other requirements than PN in more or less acute ICU situations in which patients are far from stable, most of the time hypermetabolic and/or suffering from multiple organ dysfunction. There can also be high losses of trace elements in specific disease situations for which extra compensation is needed or one has to take extra care to avoid toxic effects by accumulation of specific trace elements in case of deterioration of renal function or cholestasis.
One trace elements solution that fits all situations is not possible, but as it turned out in daily practice it offers advantages to use a standard solution to the patients with PN, supported by literature.
Providing trace elements separately means most of the time a loss of time and cost and offers more risk for increasing errors.
The compromise solution for this situation is additional supply in case of increased loss or a very high need of specific trace elements, while supplying a fixed combination of relatively low basal concentrations of the whole spectrum of trace elements preventing harm by accumulation.

In the new formulation Supliven 4 trace elements have been changed in concentration: zinc, copper, selenium and manganese. The concentrations of zinc, copper and manganese were reduced but the concentration of selenium was increased, all supported by experiences from the literature.

Zinc
The daily supply of zinc has been diminished from 100 micromole/10 ml in Addamel to 77 micromole/10 ml in the new formulation.
There is no simple way to assess the zinc nutritional status**.** No cases of clinical zinc deficiency have been reported in any patient receiving Addamel-N as part of the PN regimen. Increased loss of zinc has been documented as the result of an increased catabolism of skeletal muscles with loss of intracellular contents, including zinc in the urine, or by loss through the skin in severely burned patients and other situations. Based on studies from the literature it has been demonstrated that an intake of 40 – 60 micromole/day is required to maintain balance in stable adults. Taking into account many situations with some higher need of zinc the Aspen guidelines (2012) recommends a range of

2.5 – 5.0 mg/day well corresponding to the level of 77 micromole of a daily Supliven ampoule. This level is still 50% in access of basal requirements in most patients with PN and because it was felt to be inappropriate to provide an excess to most patients it was decided to lower the zinc supply from 100 to 77 micromole/day (or 6.5 to 5.0 mg/day).
An excess of zinc can be readily excreted in the urine or via the gut and there have been no reports of zinc toxicity as a result of Addamel-N with 100 micromole/day in the past. An upper limit of the daily dosage –to prevent any toxicology – is not known.

The MEB noted that, although there is no evidence of a gain in safety or efficacy, the decision to lower the concentration of zinc can be accepted based on the considerations of the MAH and the observations from the literature. For the large majority of patients treated with PN the basal requirements of zinc are still guaranteed while excess of zinc is avoided in more of them.

Copper
The daily supply of copper has been diminished from 20 micromole/10 ml to 6.3 micromole/10 ml in the new formulation. In the past there have been many reports of copper deficiency in patients with PN if no copper was added but no patients have ever been reported with copper deficiency if treated with Addamel-N. Individuals without a supply of copper develop reduced serum levels of copper or caeruloplasmin (although these are not sensitive markers of the copper status) or may even develop clinical signs of deficiency.
An intake of 10-20 micromole/day was found to maintain normal plasma copper levels in PN with satisfactory clinical effect supported by many reports from the literature. Nonetheless there is concern that in some patients excess copper is deposited in many tissues and will lead to accumulation in the liver with potential to cause liver damage as is known from studies in Wilson's disease. A detailed study of stable patients on PN indicated a requirement of 5-8 micromole/day and this study – regarded as the benchmark for assessing copper requirements – has led to the recommendation in the most recent version of the Aspen guidelines to reduce copper requirements to 6 micromole/day. Only if there are severe losses of copper a separate supplement may be necessary, guided by the serum copper levels. Therefore regular checks of the serum copper level during PN are mandatory.

Overall, the reduction of the copper supply from 20 to 6.3 micromole/day in the new formulation is sufficiently justified by results from the literature and the recommendation from the Aspen guideline. There is enough support from the literature that deficiency of copper will be avoided while there is less risk for harmful copper deposition.

Selenium
The daily supply of selenium has been increased from 0.4 micromole/10 ml in Addamel to 1.0 micromole/10 ml in the new formulation, Supliven. Selenium is an essential component of important extra- and intracellular nutritional antioxidant enzymes through its role in glutathione peroxidase and the levels of this enzyme may be severely depressed in septic conditions. If it is not added to PN serious deficiency may develop like skeletal myopathy and reversible to fatal cardiomyopathy. It has to be added to PN; there are no reports of deficiency with the use of Addamel-N containing 0.4 micromole/day.
However there is still considerable controversy over the requirements of selenium in health and also about which intake is necessary to maximise the plasma glutathione peroxidase activity, or even if an intake which maintains 2/3 maximum activity is sufficient. The upper estimated *dietary* requirement to maximise plasma glutathione peroxidase activity in adults seems to be 90 microgram/day, whereas the lower estimated requirement to provide only 2/3rds of this maximal activity would be 39 microgram/day.
Selenium is also potentially toxic, a reason to limit the *dietary* intake to 400 microgram/day = 5.4 micromole/day.
In home-PN (stable patients) an (i.v.) intake of 85 microgram/day has led to normal tissue concentrations. Because there may be increased need for selenium in illness a choice has been made on the basis of documentation of the effects of oral intake and the assumption that the absorption of oral selenium is about 90% which should correspond to an i.v. intake of about 80 microgram/day (= 1 micromole/day) in stead of the 0.4 micromole/day in the Addamel-N solution. This could ensure that the needs of most patients are met with the concentration in Supliven. Correction of the daily dose can be made guided by the mandatory regular checks of the serum level and/or clinical aspects.

The MEB considered that the higher selenium content of the new ampoule is an improvement of the solution because it will meet the daily requirements in many more PN patients while the concentration is still far away from possibly toxic levels. The change in concentration is justified by the information from the recent literature.

Manganese
The daily dose of manganese has been diminished of 5.0 micromole/10 ml in Addamel to 1.0 micromole/10 ml in the new formulation. Although there is remarkably few documentation regarding the effects of estimated manganese deficiency, it is generally accepted that it is an essential trace element and that a minimal concentration has to be achieved and maintained in parenteral nutrition. In adults there are no reported cases of deficiency during PN.
Since 1979 an intake of 3 – 13 micromole/day for PN has been advised and this advise was followed in the Addamel-N solution with 5 micromole/day. However, recently several reports were published mentioning accumulation of manganese in the basal ganglia of the brain as assessed by MRI technique and this could even be the case with a daily intake of 2 micromole/day, but the intakes involved and the relation to clinical effects have been highly variable (neurological signs suggestive of parkinsonism). While 2 micromole/day already may lead to elevated whole blood manganese levels and vague neurological symptoms with an increase in the MRI signal and with a daily dose of 1 micromole no elevation of the manganese level was seen, it was concluded that approximately 1 micromole/day was probably the optimal daily dose. Recently the Aspen guidelines concluded that 1.1 – 1.8 micromole/day would be safe and effective. The treating physicians still have to take care of the presence of cholestasis since manganese is normally excreted in the bile and may accumulate even with this low intake in PN.

Overall the MEB concluded that the reduction of the manganese concentration is sufficiently supported by published reports from the literature and is comparable with the most recent version (2012) of the Aspen guidelines and is potentially an improvement of the safety. An exact minimal need of manganese avoiding deficiency in stable patients is not known, but because a stable level of manganese could be achieved with the adapted dose of 1 micromole/day this dose will be adequate.

Because the presented literature revealed no clues to change the concentrations of the other trace elements in Addamel-N no comment is given on these in this report. They are still based on the well established use of Addamel-N.

IV.2 Pharmacokinetic and pharmacodynamics properties

The MAH argued that the elements and chemical components of Supliven are the same as those which have been used for Addamel-N for the past 25 years. The changes in composition will not affect the pharmacokinetic properties either of the individual elements or of the mixture as a whole.
The reduced amounts of copper, manganese and zinc have been found to be adequate to maintain plasma and red cell concentrations and therefore are expected to be sufficient to maintain the activity of intracellular enzymes. The increased amount of selenium is expected to be sufficient to maintain plasma selenium concentration and to maximise plasma glutathione peroxidase and provide better antioxidant protection. Taken together the changes in composition of Addamel-N are not expected to affect the pharmacodynamics properties of the individual elements or of the mixture as a whole.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Supliven

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity to the active substances or to one of the excipients - Risk of accumulation of trace elements
Important potential risks	--

Missing information	--

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

The benefit/risk balance of the adaptations in the concentrations of four components is considered to be positive. The former composition (Addamel-N) was approved on the basis of well established use. There has been no change in the components apart from the change in the concentration of four of them and this has no influence on the pharmacokinetic or pharmacodynamics properties. The changes in the formulation have been sufficiently supported by literature and relevant guidelines on PN, and can be approved as a line extension of Addamel-N. No clinical studies are required with Supliven.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The developed questionnaire contained 13 questions specific to Supliven and 3 specific to the format of the package leaflet.
The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Supliven, concentrate for solution for infusion has a proven chemical-pharmaceutical quality. It is an approvable line extension to Addamel-N, a well-established medicinal product with a favourable efficacy and safety profile.

The lowered concentrations of zinc, copper and manganese in the new formulation will not diminish the efficacy in preventing deficiency of these trace elements in the large majority of stable or almost stable patients treated with parenteral nutrition. At the other side certainly in case of copper and manganese (and less in case of zinc) new recognised risks of harmful organ- accumulation as published in more recent literature will be better avoided.
Regarding the increased concentration of selenium broad support can be found now in the literature and also in the guidelines that this is profitable for most patients with parenteral nutrition while there is no indication that this higher dose could be harmful.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that well-establised use of Supliven is demonstrated, and has therefore granted a marketing authorisation. Supliven, concentrate for solution for infusion was authorised in the Netherlands on 18 June 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Submission of a new or updated Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: updated certificate from an already approved manufacturer of potassium iodide.	IA	31-12-2014	5-1-2015	Approval	No