LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Addaven

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

SE/H/1449/01/MR

This module reflects the scientific discussion for the approval of Addaven. The procedure was finalised on 2015-02-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Fresenius Kabi AB has applied for a marketing authorisation for Addaven, Concentrate for solution for infusion. The active substances: chromic chloride hexahydrate, copper chloride dihydrate, ferric chloride hexahydrate, manganese chloride tetrahydrate, potassium iodide, sodium fluoride, sodium molybdate dihydrate, sodium selenite anhydrous, zinc chloride are the same as in Tracel, Concentrate for solution for infusion, marketed by Fresenius Kabi since 1987. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Addaven is presented in the form of concentrate for solution for infusion containing ferric chloride hexahydrate, zinc chloride, manganese chloride tetrahydrate, copper chloride dihydrate, sodium selenite anhydrous, sodium molybdate dihydrate, potassium iodide, chromic chloride hexahydate and sodium fluoride as active substances. The excipients are xylitol, hydrochloric acid (for pH-adjustment) and water for injections. The concentrate for solution for infusion is filled in polypropylene ampoules.

II.2 Drug Substance

Ferric chloride hexahydrate, zinc chloride, sodium molybdate dihydrate, potassium iodide and sodium fluoride have a monograph in the Ph Eur. Manganese chloride tetrahydrate, copper chloride dihydrate, sodium selenite anhydrous and chromic chloride hexahydrate does not have a monograph in the Ph Eur.

The structures of the drug substances have been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described.

The active substance specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest periods.

II.3 Medicinal Product

Addaven concentrate for solution for infusion is formulated using excipients described in the current Ph Eur. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Addaven is an updated version of the medicinal product Addamel N. In comparison to Addamel N, Addaven contains decreased concentrations of copper, manganese, and zinc and an increased concentration of selenium. With the proposed updated formula there is an increase in the exposure margins for three of the components; copper, manganese, and zinc and the only potential safety issue is the proposed increase in selenium concentration.

No new animal or in vitro studies have been performed with Addaven and a non-clinical overview based on bibliographic data has been submitted. This is acceptable.

III.2 Ecotoxicity/environmental risk assessment

Addaven concentrate for solution for infusion is not considered to represent a risk for the environment.

III.3 Discussion on the non-clinical aspects

Non-clinical data on selenium is concluded to be superseded by human data and the “non-clinical” assessment has been based exclusively on human data. A tolerable upper intake level (UL) of 300 µg Se/day was derived for adults by the European Food Safety Authority (EFSA 2006) and is considered also to apply to pregnant and lactating women. The increase in selenium content of Addaven as compared to the approved product Tracel and increase of daily intake of selenium from 32 µg to 79 µg (as Se4+) is below the proposed UL and within the limits recently recommended for parenteral nutrition by American Society for Parenteral and Enteral Nutrition; 60–100 µg/day (Vanek 2012). The increased selenium content is therefore not considered to pose any safety concerns.

There are no objections to approval of Addaven from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Addaven is a trace element solution to be given as an additive in intravenous nutrition. The active substances of Addaven have been used for many years in Tracel. The composition of Addaven is an updated formulation of Tracel.

The therapeutic indication for Addaven is to meet basal to moderately increased requirements of trace elements in intravenous nutrition. It contains the trace elements zinc, copper, iron, selenium, manganese, molybdenum, chromium, fluoride, and iodide.

IV.2 Clinical efficacy

The concentration of four of the trace elements (copper, manganese, zinc and selenium) has been adjusted, most notably manganese, to follow the results of more recent research and to follow current leading nutritional guidelines. The other trace element components in the solution (chromium, iron, molybdenum, iodide and fluoride) are left unchanged according to the same rationales.

Table 1. Trace element solution for intravenous nutrition (content of 1 ampoule)

	Original Formulation (Addamel) in 10 ml		Current Formulation (Tracel) in 10 ml		New Formulation (Addaven) 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

The use of Tracel in children weighing 15 kg and more has been approved for a considerable time. The proposed changes in concentrations seem to cover the need also in this population.

There are and will be some patients with special needs and these should be possible to identify in clinical practice.

The bibliographic references are relevant and the proposed changes are relevant.

IV.3 Clinical safety

Considering the extensive patient exposure of more than 14.5 million patients, the safety of Tracel, the precursor of Addaven, is good. The 16 reported adverse drug reactions have an uncertain relation to the product and could as well be linked to other components of the nutrition therapy, concomitant medication or underlying diseases.

The change in the composition of Addaven does not seem to change the safety profile. The composition of Addaven is in line with current international recommendations, providing a standard supply of trace elements covering most patient needs with a good safety margin.

IV.4 Discussion on the clinical aspects

The composition of Addaven, an updated formulation of Tracel, is based on recent research and recent guidelines. The references support the assumption that the benefit/risk ratio of the product will increase. The trace element needs in patients with basal parenteral nutrition therapy are judged be covered by Addaven, while maintaining a good safety margin.

Special needs in certain patient groups must be treated individually and may not benefit from this fixed trace element composition.

From a clinical perspective Addaven is recommended for approval.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 language used for the purpose of user testing the PIL was English.
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.

The risk/benefit ratio is considered positive and Addaven, Concentrate for solution for infusion, is recommended for approval.

VI. APPROVAL

The Mutual recognition procedure for Addaven, Concentrate for solution for infusion was successfully finalised on 2015-02-22.

LÄKEMEDELSVERKET
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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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