LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Viant powder for solution for infusion

(Vitamin A, Cholecalciferol (Vitamin D3), all-rac-α-tocopherol (Vitamin E), Phytomenadione (Vitamin K1), Ascorbic acid (Vitamin C), Thiamine (Vitamin B1), Riboflavin (Vitamin B2), Pyridoxine (Vitamin B6), Cyanocobalamin (Vitamin B12), Folic acid, Dexpanthenol, Biotin, and Nicotinamide)

SE/H/1691/01/DC

This module reflects the scientific discussion for the approval of Viant powder for solution for infusion. The procedure was finalised on 2018-05-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

B. Braun Melsungen AG has applied for a marketing authorisation for Viant powder for solution for infusion, 932 mg, a vitamin additive for intravenous solutions. It contains 13 water-and fat-soluble vitamins: Vitamin A, Cholecalciferol (Vitamin D3), all-rac-α-tocopherol (Vitamin E), Phytomenadione (Vitamin K1), Ascorbic acid (Vitamin C), Thiamine (Vitamin B1), Riboflavin (Vitamin B2), Pyridoxine (Vitamin B6), Cyanocobalamin (Vitamin B12), Folic acid, Dexpanthenol, Biotin, and Nicotinamide.

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The pharmacology assessment is based on literature only as no new experimental studies have been submitted.
Overall, the pharmacology studies are mostly descriptive review studies focused on the vitamins included in the medical product. However, considering the well-established use of the included vitamins, this is considered acceptable. No safety pharmacology data has been presented; however, adverse cardiovascular, CNS or respiratory effects are not expected based on the clinical experience of the vitamins.

III.2 Pharmacokinetics

Overall, as administration is via i.v., the bioavailability of the active substances in the product is considered 100%. The fat-soluble vitamins (Vitamins A, D3, E, and K1) can be accumulated to some extent and are mostly stored in the liver and adipose (fat) tissue when not used.
There is a rapid distribution of the individual vitamins contained within Viant after the i.v. infusion. When fat-soluble vitamins (Vitamin A, D, E, and K) are released from storage sites in the liver, they are transported in the blood by special carrier proteins (i.e., binding proteins: globulines, lipoproteins) to cells where they are needed. Water-soluble vitamins (ascorbic acid and the B vitamins) are stored in the body, with the exception of cyanocobalamin.
The metabolism of the vitamins contained in Viant is considered well-known and is appropriately reflected in the proposed SmPC.
Waste metabolites of the fat-soluble vitamins (Vitamin A, D3, E and K1) are generally excreted in the faeces via the bile, and some are excreted in small amounts in urine. Water-soluble vitamins (Vitamin C and the B vitamins) are excreted primarily by the urine (except for cyanocobalamine and folic acid which are excreted mainly by the bile). The excretion of most water-soluble vitamins is closely related to their intake. Hepatic function and blood flow are primary determinants of water-soluble vitamin clearance.

III.3 Toxicology

It can be concluded that the available toxicity data for the vitamins contained within Viant is incomplete and scattered across experimental animal species. However, the vitamins in the product have been in clinical use for many years and the clinical safety profiles are considered well known.
Although vitamin A in the product is a well-known developmental toxicant at high doses, the use of Viant in the proposed dosing may be considered during pregnancy.

III.4 Ecotoxicity/environmental risk assessment

The product is composed of vitamins. The Applicant has submitted a proper justification for not performing an ERA in accordance with Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2).

IV. CLINICAL ASPECTS

IV.1 Introduction

The application concerns Viant, powder for solution for infusion, a vitamin additive for intravenous solutions, ATC code: B05XC. It contains 13 water-and fat-soluble vitamins: Vitamin A, Cholecalciferol (Vitamin D3), all-rac-α-tocopherol (Vitamin E), Phytomenadione (Vitamin K1), Ascorbic acid (Vitamin C), Thiamine (Vitamin B1), Riboflavin (Vitamin B2), Pyridoxine (Vitamin B6), Cyanocobalamin (Vitamin B12), Folic acid, Dexpanthenol, Biotin, and Nicotinamide.

Viant is not identical to previously approved parenteral multivitamin products. The main differences are:

- Inclusion of Vitamin K
- Increased dose of B_1, thiamine
- Increased dose of B_6, pyroxidine
- Increased dose of B_9, folic acid
- Increased dose of Vitamin C

IV.2 Pharmacokinetics

Pharmacokinetics at the general level is presented under the heading non-clinical aspects and is equally applicable to the clinical aspects. No new data were appended the application.

IV.3 Pharmacodynamics

The pharmacodynamics of the included vitamins is considered well known and well established.

IV.4 Clinical efficacy

The applicant has submitted a thorough and in depth discussion on the efficacy of parenteral multivitamin infusions. The efficacy of the combination of included the vitamins (except Vitamin K) has been established through more than 10 years of clinical use in Europe, for the parenteral nutrition. In Europe, Vitamin K has not previously been included in multivitamins for parenteral use. Instead, Vitamin K has been included in various lipid emulsion formulations intended for parenteral administration, at a common dosage of 150 μg (0.15 mg) daily. From an efficacy point of view, the administration of vitamin K indicated for vitamin K supplementation is considered well established. For a safety discussion on the inclusion of vitamin K in the multivitamin combination, see Clinical safety.

IV.5 Clinical safety

The Viant formulation is based on “mixed micelles” consisting of glycocholic acid and lecithin as a solubiliser for the fat-soluble vitamins. Previously approved multivitamin formulation Cernevit contains the same or a similar “mixed micelle” vehicle for the solubilisation of fat-soluble vitamins. Thus, the vehicle does not cause any concerns.

Apart from an increased dose of B_1 (6.0 mg versus 3.510 mg), B_6 (6.0 mg versus 4.53 mg), B_9 (0.6000 mg versus 0.414 mg) and Vitamin C (200 mg versus 125 mg), and the inclusion of Vitamin K (0.1500 mg), the composition of Viant is in principal identical to previously approved multivitamins. The suggested increases of the water-soluble vitamins B_1, B_6, B_9 and vitamin C are at least in part based on clinical studies where it has been show that certain patient groups needed higher dosage of these vitamins to achieve desired blood or tissue concentrations. A parenteral vitamin supplementation has to be regarded as a crude and general supplementation, not necessarily adapted to each patient´s specific need; the patient population requiring vitamin supplementation is usually very heterogeneous. The vitamin requirements of critically ill patients and already deficient patient groups may differ from for example patients undergoing home parenteral nutrition. Thus, definite requirements in the different patient subgroups have not been established. Special requirements of specific vitamins have to be considered apart for a standard supplementation by the means of a multivitamin product. It is also stated in the SmPC that patients with e.g. increased requirements may need multiples of the usual daily dose of single vitamins as indicated by the clinical state. Considering that the new dosage suggested is for water-soluble vitamins (B_1, B_6, B_9 and vitamin C) with high margin of safety, the increased doses are acceptable.

A major difference in the composition of Viant and other multivitamins for parenteral use is the inclusion of vitamin K (150 µg daily). The inclusion of vitamin K entails an obvious risk that anti-coagulant activity of coumarin derivatives is weakened (usually at ≥250 µg/d vitamin K), especially if Viant is administered together with soy based lipid emulsion which are known sources of vitamin K. In the SmPC, information regarding potential interaction with anti-coagulants and the need for controlling coagulation status in the patients has been added. In addition, a warning on the outer packing has been included, to inform about the content of Vitamin K.

IV.6 Risk Management Plans

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 Viant.

Safety specification

Summary table of safety concerns

Important identified risks	None
Important potential risks	Influence on coagulation adjustment in patients on anticoagulant therapy with coumarin derivatives
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Viant powder for solution for infusion, contains 13 water-and fat-soluble vitamins (Vitamin A, Cholecalciferol (Vitamin D3), all-rac-α-tocopherol (Vitamin E), Phytomenadione (Vitamin K1), Ascorbic acid (Vitamin C), Thiamine (Vitamin B1), Riboflavin (Vitamin B2), Pyridoxine (Vitamin B6), Cyanocobalamin (Vitamin B12), Folic acid, Dexpanthenol, Biotin, and Nicotinamide).

The efficacy of the combination of 12 of the vitamins and of Vitamin K for the parenteral nutrition has been established through more than 10 years of clinical use in Europe. However, in Europe, Vitamin K has not previously been included in multivitamins for parenteral use. The inclusion of vitamin K entails an obvious risk that anti-coagulant activity of coumarin derivatives is weakened (usually at ≥250 µg/d vitamin K), especially if Viant is administered together with soy based lipid emulsion which are known sources of vitamin K. In the SmPC, information regarding potential interaction with anti-coagulants and the need for controlling coagulation status in the patients has been added. In addition, a warning on the outer packing has been included to inform about the content of Vitamin K.

The benefit/risk ratio is considered positive and Viant powder for solution for infusion, 932 mg, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Viant, powder for solution for infusion was positively finalised on 2018-05-17.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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