Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

VITAMINS B AND C INTRAVENOUS HIGH POTENCY, CONCENTRATE FOR SOLUTION FOR INFUSION

VITENTA INTRAVENOUS HIGH POTENCY, CONCENTRATE FOR SOLUTION FOR INFUSION

thiamine hydrochloride, riboflavin sodium phosphate hydrate, pyridoxine hydrochloride, ascorbic acid, nicotinamide, glucose monohydrate

PL 35533/0195

Aspire Pharma Limited

LAY SUMMARY

Vitamins B and C Intravenous High Potency, Concentrate for Solution for Infusion Vitenta Intravenous High Potency, Concentrate for Solution for Infusion

Thiamine Hydrochloride, Riboflavin Sodium Phosphate Hydrate, Pyridoxine Hydrochloride, Ascorbic Acid, Nicotinamide, Glucose Monohydrate

This is a summary of the Public Assessment Report (PAR) for Vitamins B and C Intravenous High Potency, Concentrate for Solution for Infusion and Vitenta Intravenous High Potency, Concentrate for Solution for Infusion.

It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Vitamins B and C in this lay summary for ease of reading.

For practical information about using Vitamins B and C, patients should read the Patient Information Leaflets (PILs) or contact their doctor or pharmacist.

What is Vitamins B and C and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Pabrinex Intravenous High Potency Concentrate for Solution for Infusion.

Vitamins B and C provides additional Vitamins B and C to correct deficiencies that may have occurred, for example:

- in alcoholism
- after infections
- after operations
- in certain psychiatric states.

The product is also used to maintain levels of Vitamins B and C in patients who are on long-term intermittent haemodialysis.

How does Vitamins B and C work?
Vitamins B and C are important for a number of bodily functions including releasing energy from food and in the formation of healthy skin, bones and teeth.

How is Vitamins B and C used?
The pharmaceutical form of this medicine is concentrate for solution for infusion and the route of administration is intravenous.

Vitamins B and C is given by a healthcare professional by drip infusion into a vein. The product comes in two ampoules, the contents of which are first diluted with either saline or 5% glucose solution and then given over a period of 30 minutes.

The exact dose will be decided by the patient's doctor who will monitor the patient's condition and determine what treatment is needed.

Due to the level of detail in the usage instructions it is best to refer directly to the PILs and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website for information on how this product is used.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Vitamins B and C have been shown in studies?
Vitamins B and C is a generic medicine that fulfils criteria meaning that no additional studies are required. Vitamins B and C has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics.

What are the possible side effects of Vitamins B and C?
For the full list of all side effects reported with this medicine, see Section 4 of the PILs or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PILs that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Vitamins B and C is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

Why was Vitamins B and C approved?
It was concluded that, Vitamins B and C has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Vitamins B and C?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Vitamins B and C. The RMP details the important risks of Vitamins B and C, how these risks can be minimised, any uncertainties about Vitamins B and C (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Vitamins B and C.

The information included in the SmPC and the PILs are compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Vitamins B and C are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Vitamins B and C

A marketing authorisation for Vitamins B and C was granted in the United Kingdom (UK) on 16 August 2024.

The full PAR for Vitamins B and C follows this summary.

This summary was last updated in October 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Vitamins B and C Intravenous High Potency, Concentrate for Solution for Infusion and Vitenta Intravenous High Potency, Concentrate for Solution for Infusion (PL 35533/0195) could be approved.

The product is approved in adults and children for rapid therapy of severe depletion or malabsorption of the water soluble vitamins B and C:

- particularly in alcoholism, where a severe depletion of thiamine can lead to Wernicke's encephalopathy
- after acute infections
- post-operatively
- in psychiatric states

This product can also be used to maintain levels of vitamin B and C in patients on chronic intermittent haemodialysis.

The active substances in this product are thiamine hydrochloride, riboflavin (as sodium phosphate hydrate), pyridoxine hydrochloride, ascorbic acid, nicotinamide and glucose (as monohydrate).

B vitamins play essential roles in catabolic and anabolic metabolism. They act as coenzymes in several enzymatic processes that support every aspect of cellular physiological functioning, including major functions within the brain and nervous system. Any B vitamin deficiency can negatively affect mitochondrial metabolism of amino acids, glucose, and fatty acids through the citric acid cycle and electron transport chain.

Thiamine (TPP) serves as a cofactor for many enzymes during the metabolism of glucose, proteins, and lipids. It is also a co-enzyme for pyruvate dehydrogenase, a-ketoglutarate dehydrogenase and transketolase. Thiamine deficiency leads to impaired oxidative metabolism, decreased adenosine triphoasphate (ATP) synthesis, decrease in the formation of acetylcholine for neural function and decreased energy production which in terms affects vulnerable organs such as the brain, leading to alterations in cerebral function such as utilization of glucose, alterations in neurotransmitters, oxidative stress, lactic acidosis, excitotoxicity, inflammation, endoplasmic reticulum stress and apoptosis, as well as dysfunction of the blood brain barrier

Riboflavin is a central component of the coenzymes FAD and FMN. Each of these coenzymes is essential for several reduction–oxidation enzymes and participate in synthesizing niacin, folic acid, vitamin B6, and all heme proteins. It is also needed for carbohydrate, protein, and fat metabolism into glucose. Its antioxidant effect is vital to cellular respiration and function in the immune system.

PLP, the active form of pyridoxine, is a coenzyme that supports numerous enzymes involved in the metabolism of amino acids. Such enzymes include aminotransferases, decarboxylases, and dehydratases, δ-aminolevulinate synthase in heme biosynthesis, phosphorylase in glycogen breakdown, and sphingoid base biosynthesis, etc. PLP is also a component of two enzymes that metabolize homocysteine to cysteine: Deficiency of pyridoxine leads to hyperhomocysteinemia, which is associated with thrombosis and atherosclerosis.

Nicotinamide is the precursor of NAD and NADP, which are implicated in oxidative phosphorylation and ATP production, and function as enzyme cofactors in the metabolism of macronutrients (carbohydrate, protein, and fat) and overall in at least 200 different biochemical reactions.

Vitamin C is known to be an electron donor for eight human enzymes. Probably all its biochemical and molecular functions can be accounted for by this function. Vitamin C plays an important role in eliminating oxidative stress which, in combination with its water solubility, makes it the main antioxidant of extracellular fluid. At a molecular level, vitamin C is needed in the Kreb's cycle for the formation of ATP. At a cellular level, vitamin C is involved in the synthesis of collagen and tissue healing.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Pabrinex Intravenous High Potency Concentrate for Solution for Infusion that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

A biowaiver was submitted with this application, which was accepted. No bioequivalence study was required and no new clinical studies were provided with this application.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for and Vitenta Intravenous High Potency, Concentrate for Solution for Infusion was granted in the United Kingdom (UK) on 16 August 2024.

II QUALITY ASPECTS

II.1 Introduction

This product consists of pairs of 5 ml ampoules. Each pair of ampoules to be used in treatment is labelled No. 1 and No. 2 and are described below:

Each No. 1 ampoule contains:	5 ml ampoule
Thiamine Hydrochloride	250 mg
Riboflavin (as Sodium Phosphate Hydrate)	4 mg
Pyridoxine Hydrochloride	50 mg
Each No. 2 ampoule contains:	5 ml ampoule
Ascorbic Acid	500 mg
Nicotinamide	160 mg
Glucose (as Monohydrate)	1000 mg

In addition to the active substances, this product also contain the excipients edetic acid, sodium hydroxide and water for injections.

The finished product is packaged in pairs of amber glass ampoules of 5 ml. Packs contain either six or ten pairs of 5 ml ampoules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

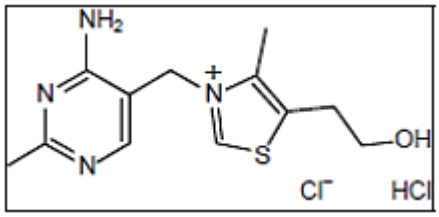
II.2 ACTIVE SUBSTANCES

rINN: Thiamine hydrochloride

Chemical Name: 3-[(4-amino-2-methyl-5-pyrimidinyl)-methyl]-5-(2-hydroxy-ethyl)-4-methyl-1,3-thiazol-3-ium chloride hydrochloride

Molecular Formula: $C_{12}H_{17}ClN_4OS \bullet HCl$

Chemical Structure:



Molecular Weight: 337.28 g/mol

Appearance: White or almost white powder

Solubility: Freely soluble in water (approx. 100 g per 100 mL), soluble in glycerol, slightly soluble in alcohol, and practically insoluble in ether, chloroform and acetone

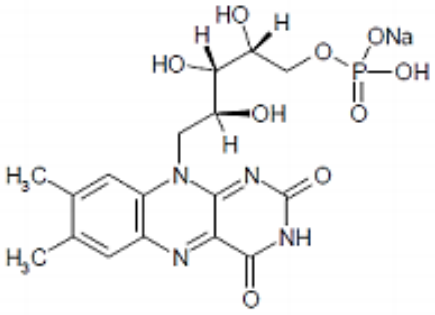
Thiamine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Riboflavin sodium phosphate hydrate

Chemical Name: 1) Riboflavin-5'-phosphoric acid ester monosodium salt
2) [D-ribo-2,3,4-trihydroxy-5-(2,3,4,10-tetrahydro-7,8-dimethyl-2,4-dioxobenzo[g]pteridin-10-yl)pentyl]-dihydrogenphosphate monosodium salt
3) Riboflavin-5'-(dihydrogenphosphate) monosodium salt

Molecular Formula: $C_{17}H_{20}N_4NaO_9P$



Chemical Structure:

Molecular Weight: 478.33 g/mol

Appearance: Yellow to orange powder

Solubility: Soluble in water (approx. 3 g/100 mL), very slightly soluble in alcohol, and practically insoluble in ether, chloroform and acetone

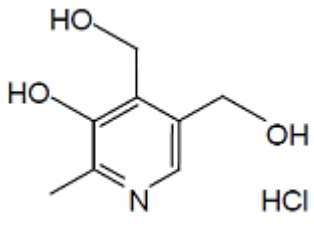
Riboflavin sodium phosphate hydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Pyridoxine hydrochloride

Chemical Name: 1) 2-methyl-3-hydroxy-4,5-bis (hydroxymethyl) pyridine hydrochloride;
2) 5-hydroxy-6-methyl-3,4-pyridinedimethanol hydrochloride;
3) 5-hydroxy-6-methyl-3,4-pyridinecarbinol hydrochloride;
4) 4,5-bis (hydroxymethyl)-2-methylpyridine-3-ol hydrochloride

Molecular Formula: $C_8H_{11}NO_3 \bullet HCl$



Chemical Structure:

Molecular Weight: 205.64 g/mol

Appearance: White or almost white powder

Solubility: Freely soluble in water (approx. 20 g per 100 mL), slightly soluble in ethanol, and insoluble in ether and chloroform

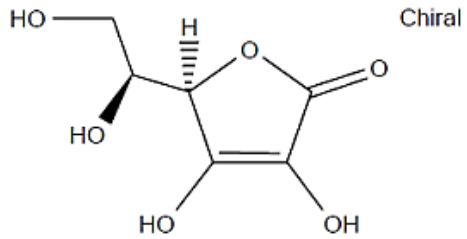
Pyridoxine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Ascorbic acid

Chemical Name: L-threo-hex-2-enoic acid g-lactone; 3-oxo-L-gulofuranolactone (enol form)

Molecular Formula: $C_6H_8O_6$



Chemical Structure:

Molecular Weight: 176.13 g/mol

Appearance: White to slightly yellow crystalline powder

Solubility: Freely soluble in water (approx. 30 g per 100 mL), sparingly soluble in alcohol (approx. 2 g per 100 mL) and practically insoluble in ether, petroleum ether, chloroform, oils and fats.

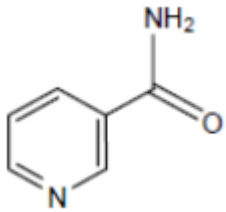
Ascorbic acid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Nicotinamide

Chemical Name: Pyridine 3-carboxamide; pyridine 3-carboxylic acid amide

Molecular Formula: $C_6H_6N_2O$



Chemical Structure:

Molecular Weight: 122.1 g/mol

Appearance: White or almost white, crystalline powder or colourless crystals

Solubility: Freely soluble in water (691.0 g/L at 20.0 °C) and in alcohol, soluble in glycerol, and very slightly soluble in ether or chloroform

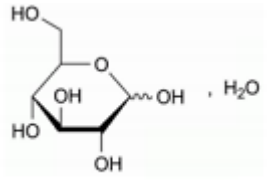
Nicotinamide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Glucose monohydrate

Chemical Name: D-glucose, Hydrate

Molecular Formula: $C_6H_{12}O_6 \cdot H_2O$



Chemical Structure:
Molecular Weight: 198.2
Appearance: White crystalline powder, odorless.
Solubility: Freely soluble in water, very slightly soluble in ethanol (96%).

Glucose monohydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, the below shelf-life and storage conditions are acceptable.

> **Before opening:** 2 years; Do not store above 25ºC. Keep the container in the outer carton. Do not freeze.

After opening: Chemical and physical in-use stability of intravenous high potency vitamins B and C has been demonstrated in the following intravenous infusion fluids for the number of hours stated in the table below, at room temperature:

Intravenous infusion fluid	In the light
Glucose 5%	7 hours
Physiological saline (sodium chloride 0.9%)	7 hours
Glucose 4.3% with sodium chloride 0.18%	4 hours
Glucose 5% with potassium chloride 0.3%	4 hours
Compound sodium lactate	7 hours

Although no further specific data are available, the solutions are expected to be stable for longer periods when protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions. The diluted solutions should not be frozen.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of riboflavin are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version(s) of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of the active substances is well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV. 2 Pharmacokinetics

No new pharmacokinetic data were submitted for this application and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

No new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Pabrinex Intravenous High Potency Concentrate for Solution for Infusion.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflets (PILs) were provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with riboflavin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflets (PILs) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK versions of the SmPC and PILs for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**