COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Junyelt, concentrate for solution for infusion

(zinc gluconate, copper gluconate, manganese gluconate, potassium iodide and sodium selenite)

NL/H/4587/001/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Junyelt, concentrate for solution for infusion. The procedure was finalised in the United Kingdom (UK/H/5859/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

JUNYELT, CONCENTRATE FOR SOLUTION FOR INFUSION

(zinc gluconate, copper gluconate, manganese gluconate, potassium iodide, sodium selenite)

Procedure No: UK/H/5859/001/DC

UK Licence No: PL 14434/0033

Laboratoire AGUETTANT

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

JUNYELT, Concentrate for solution for infusion
(zinc gluconate, copper gluconate, manganese gluconate, potassium iodide, sodium selenite)

This is a summary of the public assessment report (PAR) for JUNYELT, Concentrate for solution for infusion (PL 14434/0033; UK/H/5859/001/DC). It explains how the application for JUNYELT, Concentrate for solution for infusion 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 JUNYELT, Concentrate for solution for infusion.

For practical information about using JUNYELT, Concentrate for solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is JUNYELT, Concentrate for solution for infusion and what is it used for?
JUNYELT, Concentrate for solution for infusion is a medicine with a 'well-established use'. This means that the medicinal use of the active substances of this product has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

JUNYELT, Concentrate for solution for infusion is used to provide trace elements to preterm and term newborns, infants and children who cannot eat normally and need intravenous (into a vein) feeding.

How does JUNYELT, Concentrate for solution for infusion work?
This medicine is a concentrate for solution for infusion, especially designed for preterm and term newborns, infants and children. It contains the trace elements zinc, copper, manganese, iodine and selenium. These trace elements are essential because the body cannot produce them but needs them in very small quantities in order to function properly.

How is JUNYELT, Concentrate for solution for infusion used?
This medicine can only be obtained with a prescription.

JUNYELT, Concentrate for solution for infusion will be given intravenously (into a vein) by infusion (IV drip) by a nurse or doctor. They will decide on the correct dose.

The dosage for preterm, and term newborns, infants and children (weighing 20 kg or less) is 1 mL per kg body weight per day to a maximum daily dose of 20 ml.

For children (weighing more than 20 kg), a daily dose of 20 ml should meet basal trace element requirements.

JUNYELT, Concentrate for solution for infusion should be supplemented with a single zinc injectable solution when administered to preterm infants, to reach a total zinc parenteral intake of 450-500 µg/kg/day. A daily iron infusion is recommended when preterm infants are receiving long term parenteral nutrition (> 3 weeks), and a molybdenum add-on is recommended in case of parenteral nutrition > 4 weeks.

JUNYELT should not be administered directly to a patient but must be diluted before use.

What benefits of JUNYELT, Concentrate for solution for infusion have been shown in studies?
As zinc gluconate, copper gluconate, manganese gluconate, potassium iodide and sodium selenite are

well-known substances and their use in the licensed indications is well established, the applicant has presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the active substances for use in the licensed indications.

What are the possible side effects of JUNYELT, Concentrate for solution for infusion?
Like all medicines, this medicine can cause side effects, although not everybody gets them.
For the full list of side effects reported with JUNYELT, Concentrate for solution for infusion, see section 4 of the package leaflet, available on the MHRA website.

For the full list of restrictions, see the package leaflet.

Why was JUNYELT, Concentrate for solution for infusion approved?
The MHRA concluded that, in accordance with EU requirements, the benefits of JUNYELT, Concentrate for solution for infusion outweigh the identified risks and recommended that the product be approved for use.

What measures are being taken to ensure the safe and effective use of JUNYELT, Concentrate for solution for infusion?
A risk management plan has been developed to ensure that JUNYELT, Concentrate for solution for infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for JUNYELT, Concentrate for solution for infusion, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about JUNYELT, Concentrate for solution for infusion
Denmark, Ireland, Italy, France, Spain, the Czech Republic, Germany, Greece, Poland, the Netherlands, Finland, Norway, Portugal, Sweden, Luxembourg, Belgium, Austria and the UK agreed to grant a Marketing Authorisation for JUNYELT, Concentrate for solution for infusion (PL 14434/0033) on 12 December 2016. A Marketing Authorisation was granted in the UK on 10 January 2017.

The full PAR for JUNYELT, Concentrate for solution for infusion follows this summary. For more information about treatment with JUNYELT, Concentrate for solution for infusion, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2017.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for JUNYELT, Concentrate for solution for infusion (PL 14434/0033; UK/H/5859/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Denmark, Ireland, Italy, France, Spain, the Czech Republic, Germany, Greece, Poland, the Netherlands, Finland, Norway, Portugal, Sweden, Luxembourg, Belgium and Austria as Concerned Member States (CMS).

This product is a prescription only medicine (legal classification POM).

This was an application made under the Decentralised Procedure (DCP), according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

JUNYELT, Concentrate for solution for infusion is used as part of the intravenous nutrition of preterm and term newborns, infants and children. It is intended to meet the basal requirements for trace elements.

This product contains the active substances zinc gluconate, copper gluconate, manganese gluconate, potassium iodide and sodium selenite. These substances contain trace elements which are normally derived from a balanced diet and are necessary to maintain the metabolic equilibrium. During artificial nutrition, the supply of trace elements is necessary because a deficiency of any one of them can generate important metabolic and clinical disturbances. The composition of this medicine is based on current international recommendations regarding the requirements for trace elements in infants and children.

No new clinical or non-clinical studies were conducted, which is acceptable given that these are bibliographic applications for products containing active ingredients of well-established use.

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

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

The RMS and CMS considered that the application could be approved at the end of procedure on 12 December 2016. After a subsequent national phase, a licence was granted in the UK on 10 January 2017.

II QUALITY ASPECTS

II.1 Introduction

JUNYELT, Concentrate for solution for infusion is a clear, colourless solution with a density of 1.0, a pH of 2.7 to 3.3, an osmolality of 15 mosmol/kg and an osmolarity of 15 mosmol/L.

The solution contains 697.0 µg/ml zinc gluconate, 142.8 µg/ml Copper gluconate, 4.052 µg/ml manganese gluconate, 1.308 µg/ml potassium iodide and 4.381 µg/ml sodium selenite.

Other ingredients consist of the pharmaceutical excipients, namely hydrochloric acid (for pH adjustment) and water for injections.

The finished product is packaged in a polypropylene ampoule (10 ml per ampoule) in pack sizes of 10 and 50 ampoules. Not all pack sizes may be marketed.

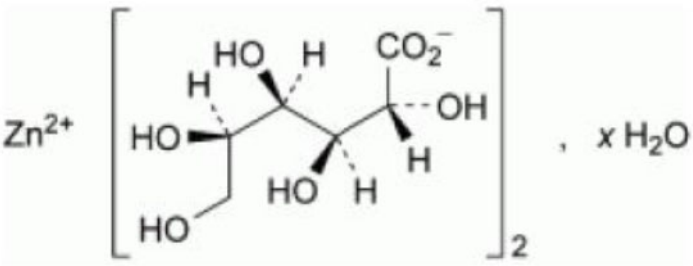
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

rINN: **Zinc gluconate**

Chemical name: Zinc gluconate
Zinc bis(D-gluconato-O^{12},O)

Structural formula:



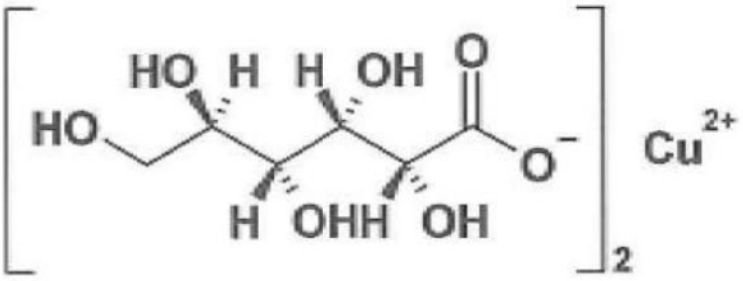
Molecular formula: $C_{12}H_{22}O_{14}Zn$, x H_2O
Molecular weight: 455.68 (anhydrous)
Appearance: White or almost white, hygroscopic, crystalline powder.
Solubility: Soluble in water, practically insoluble in anhydrous ethanol and in methylene chloride.

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

rINN: **Copper gluconate**

Chemical name: Copper bis(D-gluconato-O1, O2)-
Copper D-gluconate (1:2)

Structural formula:



Molecular formula: $C_{12}H_{22}O_{14}Cu$
Molecular weight: 453.84
Appearance: Blue green powder.
Solubility: Soluble in water, practically insoluble in ethanol, methanol and toluene, insoluble in acetone and chloroform

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

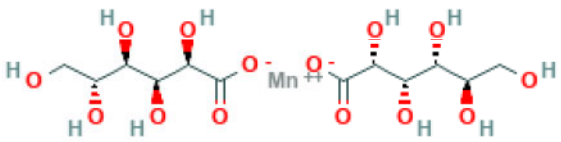
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

rINN: **Manganese gluconate**
Chemical name: Manganese D-gluconate
Bis(D-gluconato-O1,O2)manganese
Structural formula:



Molecular formula: $C_{12}H_{22}MnO_{14}$
Molecular weight: 445.232
Appearance: White or pale pink crystalline powder

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

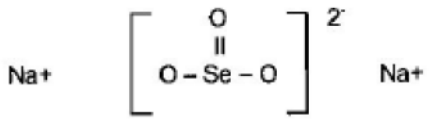
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

rINN:	**Potassium Iodide**
Chemical name:	Potassium iodide
Molecular formula:	KI
Molecular weight:	166.00
Appearance:	White or almost white powder or colourless crystals
Solubility:	Soluble in water, slightly soluble in ethanol

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

rINN:	**Sodium Selenite**
Chemical name:	Sodium selenite
Structural formula:	



Molecular formula:	Na_2SeO_3
Molecular weight:	172.94
Appearance:	White crystalline powder
Solubility:	Soluble in water

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant

Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate an aqueous, sterile and pyrogen free solution of five trace elements, packaged in 10 ml polypropylene ampoules

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacturing Process

A Satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. The manufacturing process has been validated using three industrial-scale batches of product and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the product

Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 24 months with the special storage conditions of "Do not freeze".

After dilution, chemical and physical in-use stability has been demonstrated for 48 h at 25°C. From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

II.4 Discussion on chemical, pharmaceutical and biological aspects

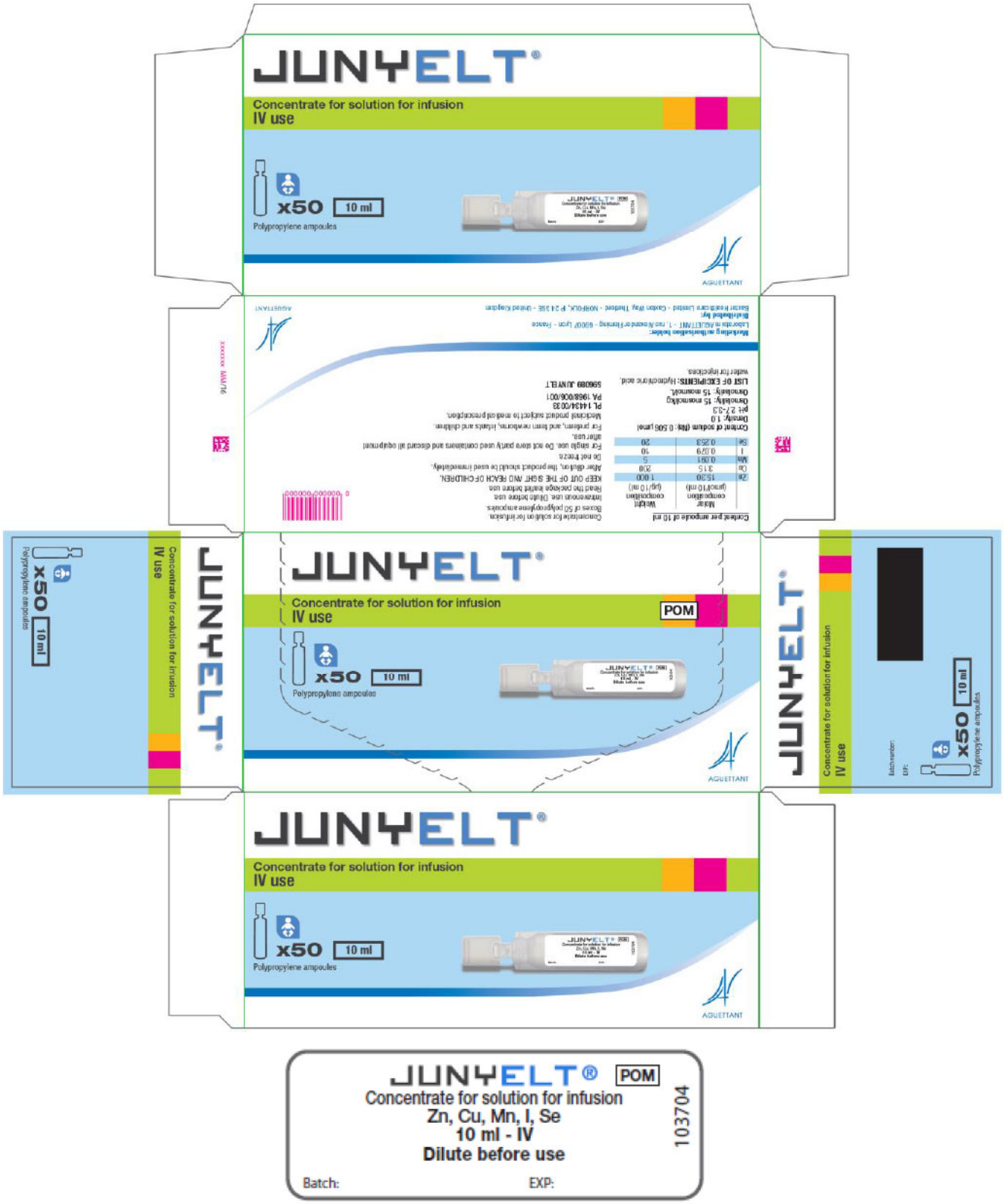
It is recommended that a Marketing Authorisation is granted for JUNYELT, Concentrate for solution for infusion.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current versions of the SmPC and PIL are available on the MHRA website.

The approved label is shown below.


JUNYELT®
Concentrate for solution for infusion
IV use
x50
10 ml
Polypropylene ampoules
AGUETTANT
POM
Batch:
EXP:
103704

III NON-CLINICAL ASPECTS

III.1 Introduction

JUNYELT, concentration for solution is composed of the trace elements zinc, copper, manganese, iodide and selenium, which are dietary minerals required in minute quantities for normal physiological function. Administration of trace elements is recognised as a standard of care for achieving adequate parenteral nutrition in patients and their clinical benefits are well-established. As such, the Applicant has not provided additional non-clinical studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

The product contains a mixture of trace elements, which are dietary minerals required in minute quantities for normal physiological function. They collectively comprise less than 1% of total body mass. Due to their involvement in many metabolic processes, trace elements are essential micronutrients that are necessary for normal health. An adequate intake of trace elements is necessary to prevent deficiency states, which can result in serious metabolic and clinical disorders.

Trace element solutions for intravenous administration are well-known products that have been used for medical purposes for many decades. These solutions are provided to patients who are not able to maintain their nutritional status by oral intake. Routine administration of trace elements is recognised as a standard of care for parenteral nutrition in patients and their clinical benefits are well-established.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

The absorption, distribution and excretion of each of the five trace elements are reviewed in the applicant's non-clinical overview.

The trace elements are absorbed to various extents after oral administration, but the product is administered intravenously and therefore all of the elements are 100% bioavailable. They are transported in the blood by proteins (manganese, copper, zinc and selenium by albumin, copper by ceruloplasmin and selenium by selenomethionine) or non-protein carriers (iodine). They are stored in specific protein/tissues (iodine in thyroid, selenium in selenoproteins and copper, zinc and manganese in metallothioneins). They are eliminated via the bile or urine, depending on the nature of the element, with cationic compounds mainly excreted via the bile and anionic elements via the urine.

III.4 Toxicology

The effects of excess trace elements are well known, and the literature on the acute and chronic toxicity, genotoxicity, carcinogenicity and reproductive toxicity of each of the five elements has been adequately reviewed in the applicant's non-clinical overview.

Although not discussed in the non-clinical overview, there are no general issues raised with respect to impurities and excipients in the drug product, and no issues have been raised in relation to extractables and potential leachables.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

An acceptable justification has been provided for the absence of an environmental risk assessment, based on the nature of the active substances being trace elements, which can therefore be considered exempt from requiring an ERA, as they are unlikely to result in significant risk to the environment. This is in accordance with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2*), and is acceptable.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for JUNYELT, Concentrate for solution for infusion.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new clinical data have been submitted and none are required for applications of this type. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of the use of trace elements for intravenous administration. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

JUNYELT concentrate for solution for infusion is a solution containing multiple trace elements. It is to be used as part of an intravenous nutrition regimen for both preterm and term newborns, infants and children. The product is intended to cover the basal trace element requirements during paediatric parenteral nutrition.

Trace element solutions for intravenous administration are well-known products that have been used for medical purposes for many decades, with several trace element formulations for adult and paediatric parenteral nutrition available in the European Union.

JUNYELT concentrate for solution for infusion has been formulated according to the latest guidelines on paediatric parenteral trace element requirements.

IV.2 Pharmacokinetics

No new pharmacokinetic data were submitted with this application and none were required as the product contains active substances that have been in clinical use for many years and the clinical pharmacology is well-known.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted with this application and none were required as the product contains active substances that have been in clinical use for many years and the clinical pharmacology is well-known.

IV.4 Clinical efficacy

No new efficacy data are presented for this application and none are required. The applicant has provided an extensive review of study reports published in the literature confirming the efficacy and safety regarding the use of this product and related products for supplementation in various deficiency states.

IV.5 Clinical Safety

The applicant has provided a literature safety review of this product and other similar products. No new safety issues have been identified.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The applicant has submitted a risk management plan (RMP), 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 JUNYELT, Concentrate for solution for infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Copper and/or Manganese toxicity related to administration in patients with pronounced cholestasis	Proposed text in SmPC: Section 4.4 (Special warnings and precautions for use) Blood manganese levels should be regularly monitored in case of prolonged artificial nutrition. A dose reduction may be necessary or infusion of NUTRYELT PAEDIATRIC should be stopped if manganese levels rise into the potentially toxic range (please refer to appropriate reference ranges). The occurrence of neurological signs must evoke the possibility of a manganese overdose. Particular attention must be paid when the product is given to patients with reduced biliary excretion, since it could interfere with the biliary elimination of manganese, copper and zinc, leading to accumulation and overdose. Copper overdose must be considered in the presence of nausea, vomiting, gastralgia. In patients with hepatic impairments or mild cholestasis the posology should be adapted.	None proposed
Copper toxicity related to administration in patients with Wilson's disease	Proposed text in SmPC: Section 4.3 (contraindications): In case of Wilson's disease	None proposed
Hypersensitivity	Proposed text in SmPC: Section 4.3 (contraindications): Patients with known hypersensitivity to one of the actives substances or to the excipients.	None proposed

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for JUNYELT, Concentrate for solution for infusion.

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, as amended. 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

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

Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

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)