COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mycofenolaatmofetil Accord 500 mg powder for concentrate for solution for infusion

(zinc gluconate, copper gluconate, manganese gluconate, sodium fluoride, potassium iodide, sodium selenite, sodium molybdate, chromium chloride and ferrous gluconate)

NL/H/4568/001/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Mycofenolaatmofetil Accord 500 mg powder for concentrate for solution for infusion. The procedure was finalised in the United Kingdom (UK/H/5396/001/E01). 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

Mutual Recognition Procedure

NUTRYELT, concentrate for solution for infusion

(zinc gluconate, copper gluconate, manganese gluconate, sodium fluoride, potassium iodide, sodium selenite, sodium molybdate, chromium chloride and ferrous gluconate)

Procedure No: UK/H/5396/001/E01

UK Licence No: PL 14434/0022

Laboratoire AGUETTANT

LAY SUMMARY

NUTRYELT, concentrate for solution for infusion
(zinc gluconate, copper gluconate, manganese gluconate, sodium fluoride, potassium iodide, sodium selenite, sodium molybdate, chromium chloride, ferrous gluconate)

This is a summary of the public assessment report (PAR) for NUTRYELT, concentrate for solution for infusion (UK/H/5396/001/E01; PL 14434/0022). It explains how NUTRYELT, 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 NUTRYELT, concentrate for solution for infusion

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

The product may be referred to as NUTRYELT in this report.

What is NUTRYELT and what is it used for?
NUTRYELT is a concentrate for solution for infusion that contains zinc, copper, manganese, fluorine, iodine, selenium, molybdenum, chromium and iron, which are essential trace elements.

NUTRYELT is a medicine with 'well-established use'. This means that the medicinal use of the active substances of NUTRYELT is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

NUTRYELT is used to provide trace elements in adults needing intravenous (into a vein) feeding.

How does NUTRYELT work?
The active substances in NUTRYELT provide a nutritional source of the essential trace elements copper, manganese, fluorine, iodine, selenium, molybdenum, chromium, zinc and iron. These trace elements ensure that the body's metabolism functions properly. The trace elements are considered as essential because the body cannot produce them but needs them in small quantities in order to function properly.

How is NUTRYELT used?
NUTRYELT is a concentrate for solution for infusion. After dilution, NUTRYELT is administered into a vein by a health professional.

A doctor will determine the right dose for the patient.The recommended daily dose is one ampoule (10 ml) of NUTRYELT. The doctor may prescribe up to 2 ampoules per day.

Use in children
NUTRYELT must not be used in children.

NUTRYELT can only be obtained on prescription.

For further information on how NUTRYELT is used, please see the package leaflet and Summary of Product Characteristics available on the MHRA website.

How has NUTRYELT been studied?
As the active substances are well-known substances, and their use in zinc, copper, manganese, fluorine, iodine, selenium, molybdenum, chromium and iron supplementation is well established, the applicant presented data from the scientific literature. The literature confirmed the efficacy and safety of zinc, copper, manganese, fluorine, iodine, selenium, molybdenum, chromium and iron supplementation in

conditions where there is increased trace element requirements in adult parenteral nutrition.

What are the possible side effects of NUTRYELT?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side-effect has been experienced after NUTRYELT has been administered:
Frequency not known (cannot be estimated from the available data): pain at the application site.

Cases of hypersensitivity reactions including fatal anaphylactic reactions have been reported in patients receiving IV iron-containing products.

For further information on side effects when NUTRYELT is used, please see the package leaflet and Summary of Product Characteristics available on the MHRA website.

Why is NUTRYELT approved?
The use of NUTRYELT in the treatment of conditions associated with increased copper, manganese, fluorine, iodine, selenium, molybdenum, chromium, zinc and iron requirements in adult parental nutrition deficiency is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of NUTRYELT outweigh the risks and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of NUTRYELT?
A Risk Management Plan has been developed to ensure that NUTRYELT 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 NUTRYELT including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about NUTRYELT
On 26 June 2014, Germany, France, Poland and the UK agreed to grant a Marketing Authorisation for NUTRYELT via the Decentralised Procedure (UK/H/5396/001/DC; PL 14434/0022). A Marketing Authorisation was granted in the UK on 23 July 2014.

A second-wave mutual recognition procedure (UK/H/5396/001/E01) involving the Concerned Member States (CMSs) Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, Greece, Italy, Luxemburg, Norway, Republic of Ireland, Spain, Sweden, , The Netherlands was concluded on 8 November 2015.

The full PAR approved for NUTRYELT follows this summary**.**

For more information about treatment with NUTRYELT, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2016.

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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 NUTRYELT concentrate for solution for infusion (PL 14434/0022; UK/H/5396/001/E01) is approvable. The product is a prescription-only medicine (POM) and is used as part of an intravenous nutrition regimen, to cover basal or moderately increased trace element requirements in parenteral nutrition. The product may be referred to as NUTRYELT in this report.

NUTRYELT is a solution composed of nine essential trace elements, namely zinc (Zn; as zinc gluconate) copper (Cu; as copper gluconate), manganese (Mn; as manganese gluconate), fluorine (F; as sodium fluoride), iodine (I; as potassium iodide), selenium (Se; as sodium selenite), molybdenum (Mo; as sodium molybdate dihydrate), chromium (Cr; as chromium chloride hexahydrate) and iron (Fe; as ferrous gluconate), which are necessary to maintain the metabolic equilibrium. Trace elements are normally derived from a balanced diet, but the need increases in cases of insufficient supply or abnormal loss, hypercatabolism (e.g. surgery, major trauma, burns), and in cases of poor absorption (e.g. short bowel disease).

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 NUTRYELT is based on current international recommendations regarding the requirements for trace elements.

The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use. The Applicant has two similar products - NONAN and DECAN which have been marketed in the EU (France) since 1985 and 1999 respectively. The qualitative composition in trace elements (TE) is similar to DECAN (although colbalt is absent). Quantitatively the composition is different. NUTRYELT solution has been formulated according to the latest guidelines on adult parenteral TE requirements.

A licence was originally granted for NUTRYELT concentrate for solution for infusion via the Decentralised Procedure (UK/H/5396/001/DC), with the UK as the Reference Member State (RMS) and Germany, France and Poland as Concerned Member States (CMSs).

A second-wave mutual recognition procedure (UK/H/5396/001/E01) involving the CMSs, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, Greece, Italy, Luxemburg, Norway, Republic of Ireland, Spain, Sweden, and The Netherlands was concluded on 8 November 2015.

Bibliographic literature data on the active ingredients have been submitted to support this application. As the application is based upon published literature it is not possible to comment on the GLP status of the studies. No new non-clinical or clinical studies were conducted to support this application, which is acceptable given that this is a bibliographic application for a product containing active ingredients of well-established use.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

First Wave DCP: The Member States, Germany, France, Poland and the UK agreed to grant a Marketing Authorisation for NUTRYELT concentrate for solution for infusion via the Decentralised Procedure (UK/H/5396/001/DC) which concluded on 26 June 2014.

Second Wave MRP: The Member States considered that the application could be approved with the end of a second-wave mutual recognition procedure (UK/H/5396/001/E01) involving the Concerned Member States (CMSs) Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, Greece, Italy, Luxemburg, Norway, Republic of Ireland, Spain, Sweden, and The Netherlands (Day 90 - 8 November 2015).

II QUALITY ASPECTS

II.1 INTRODUCTION

The finished product is a concentrate for solution for infusion.
Other ingredients consist of hydrochloric acid and water for injections. Appropriate justification for the inclusion of each ingredient has been provided.

Water for injections complies with its European Pharmacopoeia monograph. Hydrochloric acid is controlled to a suitable in-house specification. Certificates of Analysis have been provided for all ingredients, showing compliance with their respective specifications.

None of the ingredients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these ingredients.

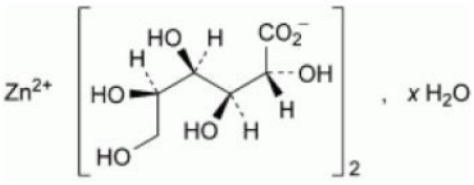
The finished product is supplied in polypropylene ampoules each containing 10 ml solution. The product is packaged with the Patient Information Leaflet in cardboard outer cartons, in pack sizes of 10, 25 and 50 ampoules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with parenteral products.

II.2 DRUG SUBSTANCES

ACTIVE SUBSTANCE - ZINC GLUCONATE

INN:	Zinc gluconate
Chemical name	Zinc bis(D-gluconato-O^1, O^2); Zinc gluconate
Molecular formula:	$C_{12}H_{22}O_{14}Zn \cdot x\ H_20$
Structure:	



Molecular mass:	455.7 g/mol
Appearance:	White or almost white, hygroscopic, crystalline powder.
Solubility:	Soluble in water, practically insoluble in anhydrous ethanol and in methylene chloride.

Zinc gluconate is the subject of a European Pharmacopoeia monograph.

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. Confirmation has been provided that the raw materials, intermediates and auxillary agents used in synthesis of the active are not of genetically modified origin. Appropriate proof-of-structure data have been supplied. 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 specifications. Batch analysis data are provided that comply with the proposed specification.

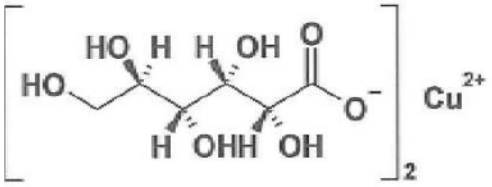
Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

ACTIVE SUBSTANCE – COPPER GLUCONATE

INN: Copper gluconate
Chemical Name: Copper bis(D-gluconato-O^1, O^2); Copper D-gluconate (1:2)
Molecular Formula: $C_{12}H_{22}O_{14}Cu$
Structure:



Molecular mass: 453.84 g/mol
Appearance: Blue green powder
Solubility Soluble in water, practically insoluble in ethanol, methanol and toluene, insoluble in acetone and chloroform.

Copper gluconate is not the subject of a European Pharmacopoeia monograph.

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. Confirmation has been provided that the raw materials, intermediates and auxillary agents used in synthesis of the active are not of genetically modified origin. Appropriate proof-of-structure data have been supplied. 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 specifications. Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

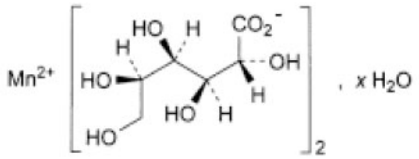
ACTIVE SUBSTANCE – MANGANESE GLUCONATE

INN: Manganese gluconate
Chemical Name: Bis(D-gluconato-O^1, O^2) manganese;

Manganese D-gluconate (1:2)

Molecular Formula: $C_{12}H_{22}O_{14}Mn \cdot xH_2O$

Structure:



Molecular mass: 445.21 g/mol

Appearance: White or pale pink, slightly hygroscopic, crystalline powder.

Solubility: Soluble in water, practically insoluble in anhydrous ethanol, insoluble in methylene chloride.

Manganese gluconate is the subject of a European Pharmacopoeia monograph.

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. Confirmation has been provided that the raw materials, intermediates and auxillary agents used in synthesis of the active are not of genetically modified origin. Appropriate proof-of-structure data have been supplied. 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 specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

ACTIVE SUBSTANCE – SODIUM FLUORIDE

INN: Sodium fluoride

Chemical Name: Sodium fluoride

Molecular Formula: FNa

Chemical Formula: NaF

Molecular mass: 41.99 g/mol

Appearance: White or almost white powder or colourless crystals.

Solubility: Soluble in water, practically insoluble in ethanol (96 per cent).

Sodium fluoride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, sodium fluoride, except for the proposed packaging specifications and stability data, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

ACTIVE SUBSTANCE – POTASSIUM IODIDE

INN: Potassium iodide

Chemical Name: Potassium iodide

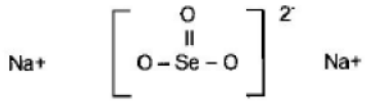
Molecular Formula:	IK
Chemical Formula:	KI
Molecular mass:	166.0 g/mol
Appearance:	White or almost white powder or colourless crystals
Solubility	Very soluble in water (1430g/l at 20°C), soluble in ethanol, freely soluble in glycerol.

Potassium iodide is the subject of a European Pharmacopoeia monograph.

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

ACTIVE SUBSTANCE-SODIUM SELENITE

INN:	Sodium selenite, anhydrous
Molecular formula:	Na_2SeO_3.
Structure:	



Molecular mass:	172.94 g/mol
Appearance:	White powder.
Solubility:	Freely soluble in water, practically insoluble in ethanol (96%) and in ether.

Sodium selenite, anhydrous is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been described adequately 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. All potential known impurities have been identified and characterised.

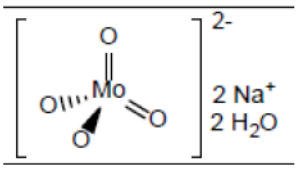
An appropriate specification is provided for the active substance. Analytical methods have been validated appropriately and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided that comply with the proposed specification.

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

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

ACTIVE SUBSTANCE - SODIUM MOLYBDATE

Compendial name	Sodium molybdate dihydrate (Ph. Eur.)
Common name:	Sodium molybdate dihydrate
Chemical name:	Sodium molybdate (VI) dihydrate
Molecular formula:	$MoNa_2O_4 \cdot 2H_2O$
Structure:	



Molecular mass:	241.95 g/mol
Appearance:	White to almost white powder or colourless crystals.
Solubility:	Freely soluble in water.

Sodium molybdate dihydrate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been described adequately 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. All potential known impurities have been identified and characterised.

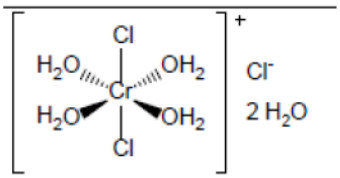
An appropriate specification is provided for the active substance. Analytical methods have been validated appropriately and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided that comply with the proposed specification.

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

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

ACTIVE SUBSTANCE – CHROMIUM CHLORIDE

Common name:	Chromium chloride hexahydrate
Chemical name:	Chromium (III) chloride hexahydrate
Molecular formula:	$Cl_3Cr \cdot 6H_20$
Structure:	



Molecular mass:	266.45 g/mol
Appearance:	Green solid (powder or crystals or chunks or a combination thereof)
Solubility:	Soluble in water, soluble in alcohol, slightly soluble in acetone and insoluble in ether

Chromium chloride hexahydrate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been described adequately 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. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been validated appropriately and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

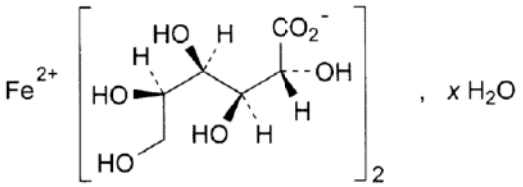
Suitable specifications have been provided for all packaging used. The primary packaging has been

shown to comply with current guidelines concerning contact with foodstuff.

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

ACTIVE SUBSTANCE – FERROUS GLUCONATE

INN:	Ferrous gluconate
Chemical name:	Iron digluconate
Molecular formula:	$C_{12}H_{22}FeO_{14}\cdot xH_2O$
Structure:	



Molecular mass:	446.1 g/mol
Appearance:	Green–yellow to grey powder
Solubility:	Freely but slowly soluble in water (100g/l at 20°C) giving a greenish-brown solution, more readily soluble in hot water, practically insoluble in ethanol (96 per cent).

Ferrous gluconate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, ferrous gluconate, except for the proposed packaging specifications and stability data, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to a produce a safe, efficacious, stable concentrate for solution for infusion for single use only, containing zinc gluconate, copper gluconate, manganese gluconate, sodium fluoride, potassium iodide, sodium selenite, sodium molybdate, chromium chloride, and ferrous gluconate.

Suitable pharmaceutical development data have been provided for this application.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described that have been validated adequately. 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

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been approved for the unopened product, with the special storage conditions "Do not freeze. Keep the container in the outer carton in order to protect from light."

From a microbiological point of view, the product should be used immediately after dilution. After

dilution, chemical and physical in-use stability has been demonstrated for 48 hours at 25°C, protected from light.

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

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this type of application for a parenteral product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of each of the nine trace elements contained in the product, namely iron (Fe), copper (Cu), zinc (Zn), manganese (Mn), chromium (Cr), selenium (Se), molybdenum (Mo), iodine (I) and fluorine (F), are well-known, no new non-clinical data have been submitted and none are required.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology of each of the nine elements contained in the product.

Suitable justification has been provided for the absence of an environmental risk assessment, in accordance with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 1*). As the active substances are trace elements, they could be considered exempt as they are unlikely to result in significant risk to the environment.

The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS
IV.1 Clinical Pharmacololgy
No new clinical pharmacology data have been submitted and none are required for this type of application. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence). A bioequivalence study was not necessary to support this application for a parenteral product, since all the substrates are available for metabolisation directly after administration.

IV.2 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 regarding the use of NUTRYELT concentrate for solution for infusion and related products supplementation in various deficiency states.

IV.3 Safety
No new safety data have been submitted with this application and none are required. The safety profiles of all the trace elements that make up NUTRYELT concentrate for solution for infusion are well known. The applicant has provided an extensive review of study reports published in the literature confirming the safety regarding the use of NUTRYELT concentrate for solution for infusion and related products supplementation in various deficiency states. No new safety issues have been identified.

IV.4 Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the Marketing Authorisation Holder (MAH), fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Risk Management Plan (RMP) is considered adequate. Routine risk minimisation is provided through the Summary of Product Characteristics and the Patient Information Leaflet and this is sufficient.

IV.5 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V User consultation

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

VI OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of NUTRYELT, concentrate for solution for infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for this type of application.

CLINICAL

No new clinical data were submitted and none are required for this application for a parenteral product. The applicant has provided an extensive review of study reports published in the literature confirming the efficacy regarding the use of NUTRYELT, concentrate for solution for infusion and related products supplementation in various deficiency states.

SAFETY

No new safety data were provided and none are required. The applicant has provided an extensive review of study reports published in the literature confirming the safety regarding the use of NUTRYELT, concentrate for solution for infusion and related products supplementation in various deficiency states. No new safety issues have been identified.

PRODUCT LITERATURE

The approved SmPC is satisfactory. The PIL and labelling are satisfactory, and consistent with the approved SmPC.

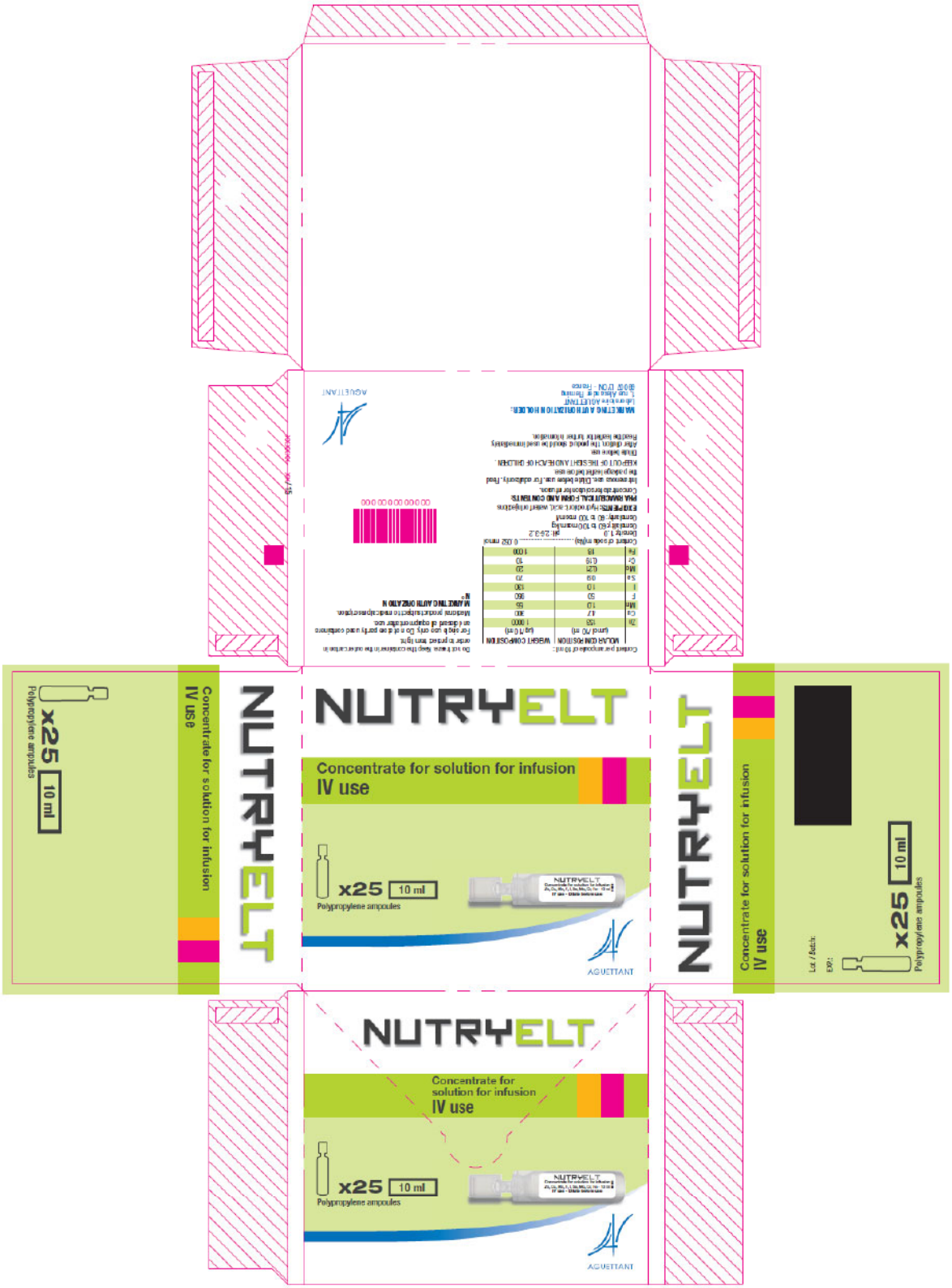
BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable. The application complies with CHMP guidance documents and contains an adequate review of published clinical data. There are no indications in the light of scientific knowledge that it differs significantly from the other similar medicinal products with regard to safety or efficacy. NUTRYELT, concentrate for solution for infusion contains widely used and well-known active substances which have a long history of established favourable benefit risk profile.

Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
The Summaries of Product Characteristics and Patient Information Leaflets (PIL) are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved labelling mock-ups are presented below:


NUTRYELT
Concentrate for solution for infusion
IV use
x25 10 ml
Polypropylene ampoules
AGUETTANT

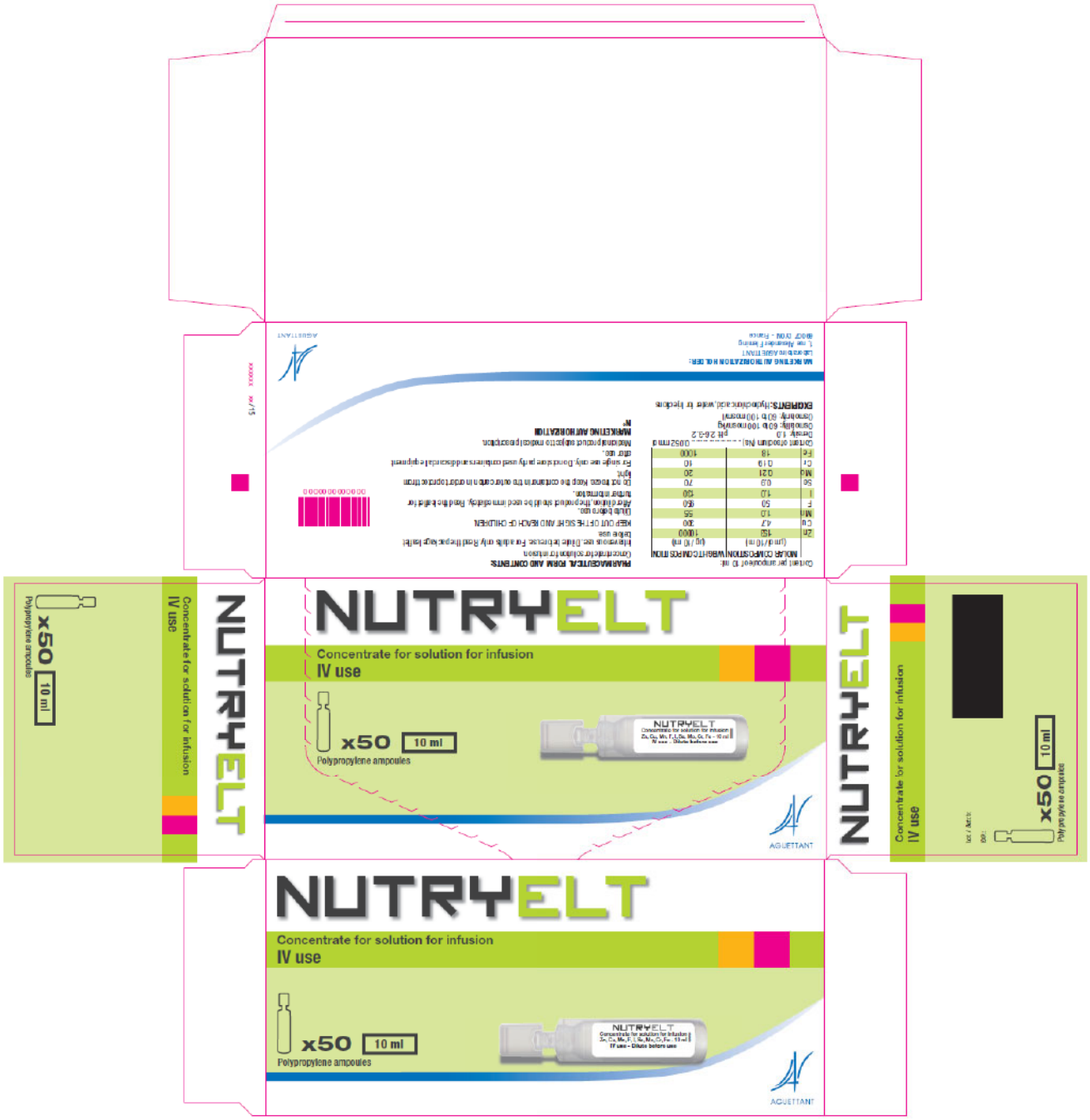

NUTRYELT
Concentrate for solution for infusion
IV use
x50
10 ml
Polypropylene ampoules
AGUETTANT

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 (Type II variations, PSURs, commitments)

The following table lists a non-safety update to the Marketing Authorisations for these products that has been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Scope	**Procedure numbers**	**Product information affected**	**Date of start of the procedures**	**Date of end of procedures**	**Approval / non approval**	**Assessment report attached Y/N (version)**
To update sections 4.1, 4.2, 4.4, 4.6, 6.1, 6.3, 6.6 of the SPC and product information resulting from comments of the new concerned members states (CMS) during a repeat use procedure.	UK/H5396/01/II/005	SmPC, PIL and lable	08/01/2016	15/08/2016	Approved	Yes

ANNEX 1

Our Reference:	PL 14434/0022-0011
Product:	NUTRYELT, concentrate for solution for infusion
Marketing Authorisation Holder:	LABORATOIRE AGUETTANT
Active Ingredient(s):	zinc gluconate, copper gluconate, manganese gluconate, sodium fluoride, potassium iodide, sodium selenite, sodium molybdate, chromium chloride, ferrous gluconate
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Standard
EU Procedure Number (if applicable):	UK/H5396/01/II/005

Reason:
To update sections 4.1, 4.2, 4.4, 4.6, 6.1, 6.3, 6.6 of the Summary of Product Characteristics (SmPC) and product information resulting from comments of the new concerned members states (CMS) during a repeat use procedure.

Supporting Evidence
Revised SmPC fragments, patient information leaflet (PIL) and labelling were provided.

Evaluation
The proposed changes to the SmPC, PIL and labelling are in line with the Quality Review of Documents (QRD) template. The updated SmPC fragments, PIL and labelling have been incorporated into the Marketing Authorisation.

Conclusion
The proposed changes to the SmPC, PIL and labelling are acceptable.

Decision - Approved on 15 August 2016.