LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Peditrace Novum
# (potassium iodide, sodium selenite anhydrous, cupric chloride dihydrate, manganese chloride tetrahydrate, zinc chloride)

# SE/H/2192/01/DC

**This module reflects the scientific discussion for the approval of Peditrace Novum. The procedure was finalised on 2023-04-18. For information on changes after this date please refer to the module 'Update'.**

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Peditrace Novum, concentrate for solution for infusion.

The active substances are potassium iodide, sodium selenite anhydrous, cupric chloride dihydrate, manganese chloride tetrahydrate and zinc chloride. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Peditrace Novum, concentrate for solution for infusion, is an application submitted according to Article 10a of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK(NI) as concerned member states (CMS).

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

**Potential similarity with orphan medicinal products**
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

# 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

**Pharmacology**
The following trace element included in the updated trace element formulation, New Ped TE (Peditrace Novum) are:

- Zinc (Zn)
- Copper (Cu)
- Iodine (I)
- Selenium (Se)
- Manganese (Mn)

Essentiality of the trace elements included in the product

*Zinc (Zn)*
A large number of zinc enzymes are essential for health and well-being. Zinc has an important role in wound healing, structural integrity of proteins, gene expression and nuclear binding proteins regulation, and acting as transcription factor.

*Copper (Cu)*
Copper is involved in connective tissue formation, iron metabolism and hematopoiesis. It is an antioxidant and involved in central nervous system function, a functional component of several copper metallo-enzymes (i.e. cupro-enzymes), including cytochrome oxidase, superoxide dismutase, amine oxidases and lysyl oxidase.

*Iodine (I)*
Iodine is an essential component of the thyroid hormones thyroxin (T4) and tri-iodothyronine (T3), necessary for cellular metabolism and maintenance of metabolic rate.

*Selenium (Se)*
Selenium is a key antioxidant, anti-inflammatory and is associated with immunological activities and functions via proteins known as selenoproteins. The most important selenoprotein is glutathione peroxidase (GSH-Px), an antioxidant which reduces cell membrane damage caused by lipid hydroperoxides and hydrogen peroxide. Selenium have been suggested to have a role in anti-inflammatory activity by inhibiting nuclear transcription factor kappa β, as well as in the regulation of thyroid hormone metabolism via three selenium dependent enzymes.

*Manganese (Mn)*
Manganese is a cofactor for several enzymes including mitochondrial superoxide dismutase and pyruvate carboxylase and is involved in activation of other enzymes such as hydrolases, kinases and transferases.

**Toxicology**
*Repeat-Dose Toxicity*
No new studies have been conducted on New Ped TE and no other studies regarding reproductive toxicity, genotoxicity, carcinogenicity have been presented.

Toxicity studies performed with TE-5, (a cocktail containing iron, copper, zinc, iodine, manganese) in rats receiving total parenteral nutrition (TNP) +TE-5 at 10 times the human clinical dose for seven days did not demonstrate any special hazards.

Given that Peditrace Novum parenteral supplementation is a well-established use product with known clinical profile and will be used within the proposed indications, this is considered acceptable from a non-clinical perspective and in accordance with the recommendations for Article 10a of Directive 2001/83/EC, as amended.

**Environmental Risk Assessment (ERA)**

A justification for not submitting an environmental risk assessment has been provided by the applicant. It is agreed that this product will not increase the exposure to the environment since it will replace existing products on the market. An environmental risk assessment is therefore not deemed necessary.

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

# IV. CLINICAL ASPECTS

**Pharmacokinetics**

No bioequivalence study has been performed to bridge to the data in the literature. This application is solely based on published literature references. Intravenous products containing similar trace elements have been used in clinical efficacy and safety studies.

Individual trace elements are taken up from the blood stream by the different target tissues to varying extents, depending on the metabolic requirement within each tissue to maintain or restore the trace element concentrations. The individual trace elements are transported in the blood by proteins (manganese, copper, zinc and selenium by albumin; copper by ceruloplasmin, iodine by thyroglobulin, and selenium by selenomethionine) or non-protein carriers. Manganese is also bound to transferrin.

In adult and paediatric patients, the trace elements excreted primarily in the urine are selenium and iodine, while copper and manganese are excreted primarily in the bile. Excretion of zinc is mainly in the faeces by transport through the intestinal mucosa, with a smaller amount in the bile and in urine. Urinary losses of zinc may increase with conditions such as starvation or trauma, and in patients who have minimal faecal excretion (for example, those receiving parenteral nutrition).

In renal disease, trace elements normally excreted by the kidneys such as selenium, iodine and partly zinc, may accumulate. In hepatic disease, excretory liver function via the bile may be decreased (especially in cases of cholestasis). This may reduce excretion of copper, zinc and manganese, with risk of their accumulation. Thus, dose adjustments might be needed in patients with impaired renal function and impaired liver function or mild cholestasis.

No clinically relevant drug-drug interactions were identified.

<u>Assessor’s overall conclusions on pharmacokinetics</u>

This is an application according to Article 10a well-established use. As this is a complete application, the bibliography should cover all aspects of pharmacokinetics needed to make a complete characterisation of the disposition of the compound. For a WEU application, it is necessary to establish a bridge between the new product and the products used in the literature to support efficacy and safety. No bioequivalence study comparing the new product to the formulations used in the literature has been conducted. This is acceptable considering the characteristics of the active substances and the drug formulation (i.e., water solution with hydrochloric acid) as well as the intended parenteral route of administration.

The Applicant has sufficiently summarized the basic pharmacokinetics of the trace elements (zinc, selenium, iodine, copper, manganese) included in Peditrace Novum.

**Pharmacodynamics**
Peditrace Novum is a mixture of naturally occurring ionic salts of the contained trace elements in amounts normally retained by the developing foetus or normally absorbed from the oral diet. Peditrace Novum has no pharmacodynamic effects besides maintaining or repleting nutritional stores within normal range. A comprehensive summary of the biological functions of the trace elements included in Peditrace Novum has been provided.

**Clinical efficacy**

*WEU*
For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the European Union for at least ten years, with recognised efficacy and an acceptable level of safety. Trace element solutions for IV administration are well-known products that have been used for medical purposes for many decades, with several TE formulations for adult and paediatric PN available in the European Union. One similar product, Peditrace, which contains all APIs of the proposed product is approved. Since its first registration in 1993 in Sweden, Peditrace has been used in over 40 countries worldwide including a total of 24 countries in the EEA. Therefore, the time over which all contained APIs have been used in the EU is longer than 25 years. Thus, the WEU criterium is considered fulfilled.

*Published literature*
The results of the published studies with Peditrace corresponded well to the provided level of the investigated trace element(s). The basic provision covered by Peditrace was sufficient for improving or maintaining serum/blood levels of the assessed trace element(s) if the recommended dose level was used. More evidence is contributed from the use of various dose levels of individual trace elements as part of parenteral nutrition. For each individual trace element contained in Peditrace Novum, additional data on the efficacy of relevant dosage was provided.

*Comparison of Peditrace Novum composition and posology versus expert recommendations*
Peditrace Novum contains zinc, copper, iodine, selenium and manganese. The proposed doses of copper, iodine and manganese are in agreement with the recommendations by ESPGHAN for all paediatric sub-groups. Regarding zinc, the proposed doses for preterm and term neonates provided by Peditrace Novum are in agreement with recommendations by ESPGHAN while the doses in children <20 kg body weight and adolescents are above ESPEN recommendations but below the maximum recommended dose of 5 mg/d for routine supplementation. For selenium, the dose for preterm neonates provided by Peditrace Novum is in agreement with recommendations by ESPGHAN while the doses in term neonates, children <20 kg body weight and adolescents are slightly above ESPGHAN recommendations.

It is noted in the ESPGHAN guideline that zinc, copper and selenium deficiency have occasionally been reported in patients on long-term PN and therefore it is recommended that levels should be monitored in patients on long-term PN.

Peditrace Novum does not include chromium, fluoride, iron or molybdenum, and acceptable justifications for their absence have been provided. Iron supplementation is generally considered unnecessary during short-term PN (<3 weeks) but recommended for patients receiving long-term PN. The SmPC section 4.2 recommends daily iron infusions to patients receiving PN for more than 3 weeks. For molybdenum, there is no need for molybdenum during short term PN but in long term PN (>4 weeks), supplementation of molybden is recommended according to the most recent ESPEN recommendations.

In summary, there is adequate evidence that the formulation and proposed posology for Peditrace Novum as part of PN covers basal daily requirements of the contained trace elements zinc, copper, iodine, selenium and manganese in all paediatric age groups. There have been no reports of trace element deficiencies occurring in patients receiving Peditrace or other products for PN at the same dose. Trace element solutions for IV infusion, like Peditrace Novum, are well-known products that have been used for medical purposes for many decades, with several trace element formulations for PN in adult and paediatric patients available in the European Union.

**Clinical safety**
The Applicant has provided publicly available data related to safety both from studies with trace element combinations (i. e. Peditrace) and individual trace elements. Post-marketing data on the predecessor product Peditrace are also referred to. Overall, the literature data suggests that trace elements at the proposed dose levels are well-tolerated, and no new safety concerns have been identified. The safety is considered well-established.

**Risk Management Plan**
The MAH has submitted a risk management plan, Version 0.1 (DLP 01-Jul-2021, date of final sign off 16-Sep-2021) 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 Peditrace Novum.

Safety specification

Proposal of safety concerns in the initial RMP version 0.1:

| **Summary of safety concerns** | |
|---|---|
| Important identified risk | None |
| Important potential risk | None |
| 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 submitted Risk Management Plan, version 0.1 signed 16 September 2021 is considered acceptable.

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

Peditrace Novum is a solution for infusion of trace elements (copper, iodide, manganese, selenium and zinc) indicated in preterm and term neonates, infants, children, and adolescents in need of IV nutrition to supply the basal requirements of trace elements. The application for Peditrace Novum concentrate for solution for infusion has been submitted according to Article 10a of Directive 2001/83/EC.

Trace element solutions for IV administration are well-known products that have been used for medical purposes for many decades, with several trace element formulations for paediatric parenteral nutrition available in the European Union. Thus, the WEU criterium is considered fulfilled.

There is adequate evidence in literature and in European expert recommendations that the formulation and proposed posology for Peditrace Novum covers basal daily requirements of the contained trace elements zinc, copper, iodine, selenium and manganese in all paediatric age groups.

There is extensive experience concerning safety of the individual trace elements and their combination. Overall, the literature data suggests that trace elements at the proposed dose levels are well-tolerated. Furthermore, the Applicant refers to post marketing experience available from the predecessor Peditrace marketed by the MAH, considered to be safe and effective with a positive benefit-risk ratio. There is no reason to believe that the safety profile of Peditrace Novum should be different.

The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

# VII. APPROVAL

The decentralised procedure for Peditrace Novum, concentrate for solution for infusion was positively finalised on 2023-04-18.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected (Yes/No) | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| | | | | | |

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

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se