



**Public Assessment Report**

**Decentralised Procedure**

**AT/H/0890/001**

**Zink Aguettant 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung**

**Former:**

**ZINC 1 MG/ML, CONCENTRATE FOR SOLUTION FOR INFUSION  
(zinc gluconate)**

**Former Procedure No: UK/H/5571/01/DC**

**UK Licence No: PL 17871/0211**

**Jenson Pharmaceutical Services Limited**

## LAY SUMMARY

### Zinc 1 mg/ml, concentrate for solution for infusion (zinc gluconate)

This is a summary of the public assessment report (PAR) for Zinc 1 mg/ml, concentrate for solution for infusion (PL 17871/0211; UK/H/5571/001/DC). It explains how Zinc 1 mg/ml, 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 Zinc 1 mg/ml, concentrate for solution for infusion.

For practical information about using Zinc 1 mg/ml, concentrate for solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

#### **What is Zinc 1 mg/ml, concentrate for solution for infusion and what is it used for?**

Zinc 1 mg/ml, concentrate for solution for infusion is a medicine with a 'well-established use'. This means that the medicinal use of the active substance of Zinc 1 mg/ml, concentrate for solution for infusion has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Zinc 1 mg/ml, concentrate for solution for infusion is used to prevent or treat deficiency when parenteral nutrition (artificial feeding through a vein) is necessary.

#### **How does Zinc 1 mg/ml, concentrate for solution for infusion work?**

This medicine contains the active substance zinc gluconate, which belongs to a group of mineral supplements and provides a nutritional source of zinc. Zinc is an essential trace element, which means the body requires only a very small quantity of this nutrient. Zinc ensures that the metabolism functions efficiently. It has an essential biological role for some organs (liver, pancreas, brain, gut), hormonal or enzymatic systems, and for defence against risk of infection (immune system). Zinc plays an important role in the growth of premature babies, infants and children with increased requirements.

#### **How is Zinc 1 mg/ml, concentrate for solution for infusion used?**

This medicine can only be obtained with a prescription.

This medicine will always be administered by a healthcare professional. A doctor will determine the dose of Zinc 1 mg/ml, concentrate for solution for infusion based on the patient's needs. Samples of patient's blood will be taken during treatment. The level of zinc in the blood will be measured to ensure it does not exceed the recommended level.

Zinc 1 mg/ml, concentrate for solution for infusion will be diluted before it is given as a slow infusion. It will be diluted in parenteral nutrition mixes or in an isotonic solution (such as sodium chloride 0.9% or glucose 5%). The treatment duration will be determined by the patient's doctor.

#### **What benefits of Zinc 1 mg/ml, concentrate for solution for infusion have been shown in studies?**

As zinc gluconate is a well-known substance and its 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 zinc gluconate for use in the licensed indications.

#### **What are the possible side effects of Zinc 1 mg/ml, 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 Zinc 1 mg/ml, 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 Zinc 1 mg/ml, concentrate for solution for infusion approved?**

The MHRA concluded that, in accordance with EU requirements, the benefits of Zinc 1 mg/ml, 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 Zinc 1 mg/ml, concentrate for solution for infusion?**

A risk management plan has been developed to ensure that Zinc 1 mg/ml, 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 Zinc 1 mg/ml, 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 Zinc 1 mg/ml, concentrate for solution for infusion**

Austria, Belgium, Germany, Denmark, Finland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Sweden and the UK agreed to grant Marketing Authorisations for Zinc 1 mg/ml, concentrate for solution for infusion (PL 17871/0211) on 27 August 2015. A Marketing Authorisation was granted in the UK on 18 September 2015.

The full PAR for Zinc 1 mg/ml, concentrate for solution for infusion follows this summary. For more information about treatment with Zinc 1 mg/ml, concentrate for solution for infusion read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2015.

## 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 Zinc 1 mg/ml, concentrate for solution for infusion (PL 17871/0211; UK/H/5571/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Belgium, Germany, Denmark, Finland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland and Sweden 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 an active substance of well-established use.

Zinc 1 mg/ml, concentrate for solution for infusion is indicated for use as a supplementation solution in prolonged parenteral nutrition and in situations where a pronounced deficiency may occur: e.g. severe malnutrition, hypercatabolism, digestive fistula, chronic diarrhoea.

This product contains the active substance zinc (as zinc gluconate). Zinc has three main biological roles: catalytic, structural and regulatory. Zinc is a component of many metalloenzymes including carbonic anhydrase, alkaline phosphatase, carboxypeptidase, oxidoreductases, transferases, ligases, hydrolases, isomerases and alcohol dehydrogenase. Zinc is also involved in the structure and stabilisation of some enzymes, such as the antioxidant superoxide dismutase. It also plays a role in the synthesis of RNA and DNA and in regulating the catabolism of RNA. Apoptosis is potentiated by zinc deficiency. Zinc affects multiple aspects of the immune system. Zinc is involved in some hormonal metabolisms (such as insulin, gustin, thymulin), and in the metabolism of carbohydrates, lipids and proteins. It has an important place in the growth of premature babies, infants and children with increased requirements. Zinc has an effect on tissue integrity and can improve the sense of taste in depleted patients. Considering all its potential biochemical activities, zinc is necessary for growth and cellular multiplication, in bone metabolism, immunity and reproduction. It contributes in protection against free radicals, inflammation and intervenes in cerebral functions. All these physiological actions can be modified by zinc deficiency.

No new clinical or non-clinical studies were conducted, which is acceptable given that this is a bibliographic application for a product containing an active ingredient 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 27 August 2015. After a subsequent national phase, a licence was granted in the UK on 18 September 2015.

## II QUALITY ASPECTS

### II.1 Introduction

Zinc 1 mg/ml, concentrate for solution for infusion is a clear colourless solution. Each ml of solution contains 6.97 mg of zinc gluconate, equivalent to 1 mg of zinc (i.e 15.29 micromoles). Each vial of 10 ml contains 69.7 mg of zinc gluconate equivalent to 10 mg of zinc (i.e 152.9 micromoles).

The finished product is packaged in a glass vial with an elastomer (bromobutyl) stopper fitted with an aluminium cover and crimped. Each vial contains 10 ml of solution and the vials are packaged in a box containing 10 vials.

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.

The only excipient in Zinc 1 mg/ml, concentrate for solution for infusion is water for injections. Water for injections complies with its European Pharmacopoeia monograph. This excipient is not sourced from animal or human origin.

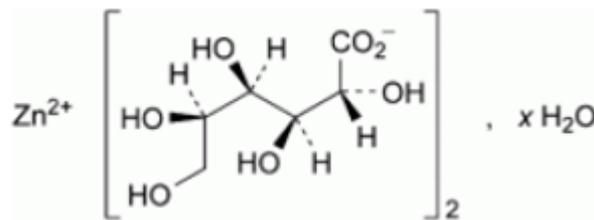
No genetically modified organisms (GMO) have been used in the preparation of this product.

### II.2 Drug substance

rINN: Zinc gluconate

Chemical name: Zinc gluconate

Structure:



Molecular formula:  $C_{12}H_{22}O_{14}Zn, xH_2O$

Molecular weight: 455.68 (anhydrous substance)

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.

### II.3 Medicinal Product

#### Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious and stable concentrate for solution for infusion, containing 1 mg/ml of zinc.

A satisfactory account of the pharmaceutical development has been provided.

## 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 3 commercial scale batches and has shown satisfactory results.

## Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. 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 30 months for the unopened vial, with the special storage conditions of "Do not freeze".

After dilution, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature. 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 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

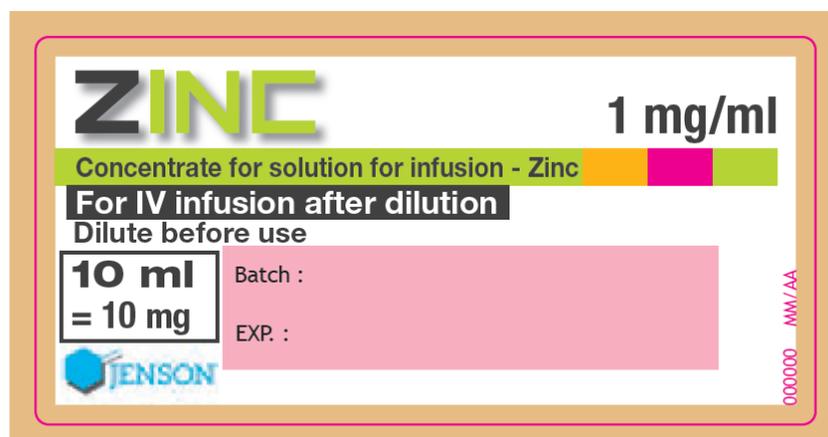
It is recommended that a Marketing Authorisation is granted for Zinc 1 mg/ml, concentrate for solution for infusion.

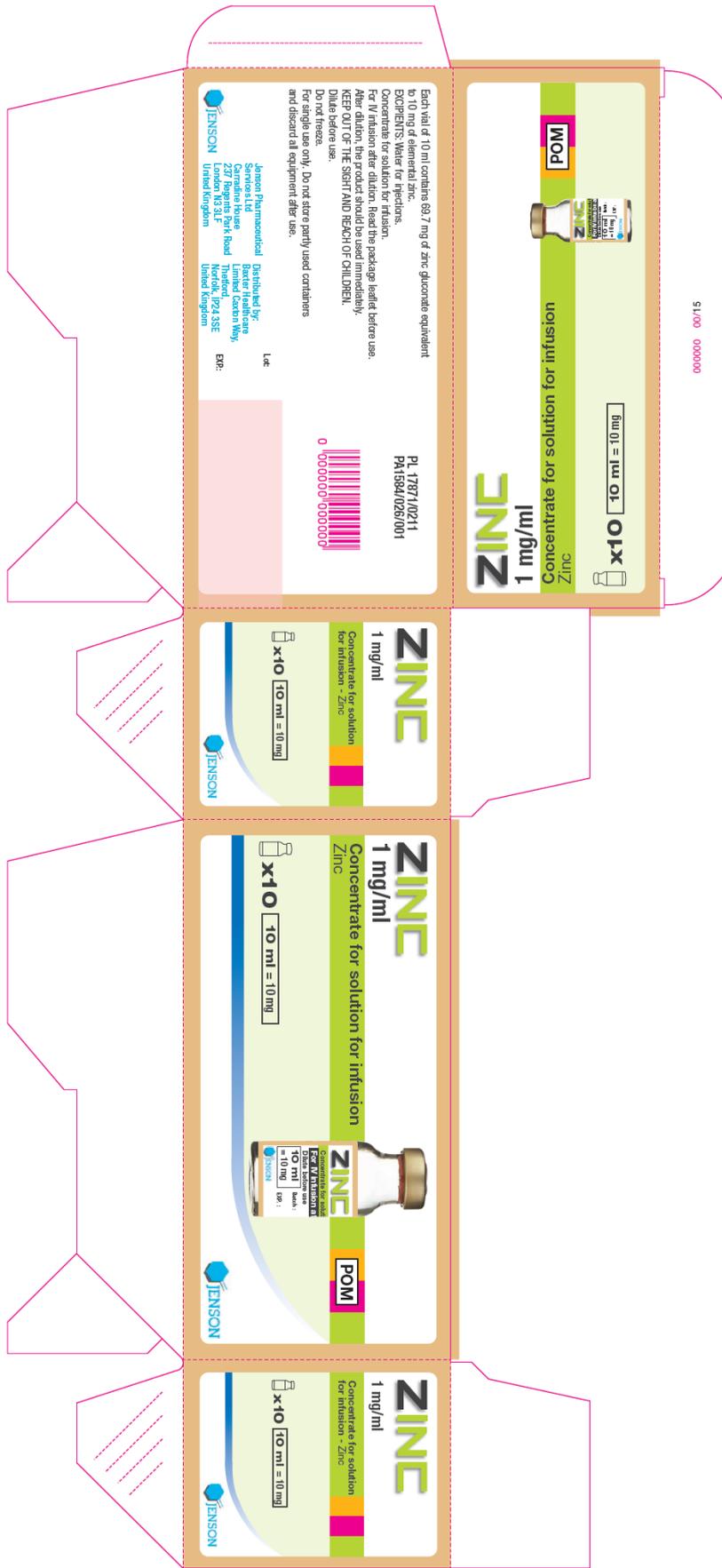
## II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

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

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

The approved labels are below:





### III NON-CLINICAL ASPECTS

#### III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of zinc gluconate are well known. No new non-clinical data have been submitted for this application and none are required.

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 applicant's non-clinical overview provides a brief summary of the pharmacology of zinc, with some emphasis on its use as a trace element in the treatment of zinc deficiency.

The overview makes a sufficient case for the necessity of zinc in supporting growth and cellular multiplication, in bone metabolism, immunity and reproduction. Zinc is essential for protection against free radicals, inflammation and for cerebral functions. It is essential for the proper functioning of the immune system, bone development, sexual function, normal taste, olfactory sensation and night vision. It plays a role in maintaining proper hormonal status and is involved in controlling the levels of insulin, thymulin, nerve growth factor, thyroid hormones, testosterone and somatomedin C. It is noted that all of these actions can be modified by zinc deficiency.

#### III.3 Pharmacokinetics

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

Zinc is absorbed to various extents after oral administration, but this product is administered intravenously and therefore will be 100% bioavailable. Zinc is distributed to all tissues including the liver, GI tract, kidney, skin, lung, brain, heart, pancreas, prostate and hippocampus. It is predominantly found in skeletal muscle (86%). High concentrations of zinc are also detected in the retina and sperm. Zinc is essential for bone mineralisation and zinc deficiency has been shown to adversely affect fetal development.

Zinc is mainly eliminated via faeces, however a small proportion may be seen in urine.

The pharmacokinetics of zinc are well established and no new concerns have been raised as a result of the review of the scientific literature.

#### III.4 Toxicology

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

Trace elements are essential micronutrients that are necessary for normal health, but in excess, they can have deleterious effects. The literature on the acute and chronic toxicity, genotoxicity, carcinogenicity and reproductive toxicity of zinc has been reviewed in the applicant's non-clinical overview.

Excessive exposure to dietary zinc is associated with poor growth and anaemia. Changes to the kidney and the pancreas have been seen in various animal species. Excessive levels of zinc are accompanied by reduced levels of copper, suggesting that some of the signs of toxicity ascribed to exposure to excess levels of zinc may be caused by zinc-induced copper deficiency.

Zinc is neither a mutagen nor a carcinogen, although weak clastogenic effects have been reported in one study. A possible association between excess or deficient zinc and carcinogenesis has been suggested; however there is no evidence to suggest that zinc poses a carcinogenic risk to humans.

Very high levels of zinc are toxic to pregnant mice and hamsters. Equally zinc is necessary for normal fetal growth and development, and fetal damage may result from zinc deficiency.

Impurities were discussed in the non-clinical overview, and separate reports were included on formic acid and glycolic acid in the quality dossier. Based on the literature reviews conducted, the limits proposed for these related substances are acceptable.

Concerns for extractables present in the final drug product due to the vial or stopper have been addressed. The presence of these extractables is considered to be safe, following the receipt of further toxicological evidence.

### **III.5 Ecotoxicity/Environmental risk Assessment (ERA)**

The Marketing authorisation Holder has provided adequate justification for not submitting an ERA. Due to the nature of the constituents of the product (trace element and water for injections) and in accordance with the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMA/CHMP/SWP/4447/001corr1), Zinc 1 mg/ml, concentrate for solution for infusion can be considered as exempted from needing an ERA because it is unlikely that the use of this medicine will result in significant risk to the environment.

### **III.6 Discussion of the non-clinical aspects**

It is recommended that a Marketing Authorisation is granted for Zinc 1 mg/ml, 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 zinc gluconate. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

### **IV.2 Pharmacokinetics**

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

Zinc is one of the most abundant trace metals in humans, it is found in all tissues and all body fluids. The total zinc content of the human body (70 kg) is in the range 1.5–3 g. Most of this is found in muscle ( $\approx 60\%$ ), bone ( $\approx 30\%$ ), skin and hair ( $\approx 8\%$ ), liver ( $\approx 5\%$ ) and gastrointestinal tract and pancreas ( $\approx 3\%$ ). In all other organ systems, the zinc content is  $\leq 1\%$ . After ingestion, zinc in humans is initially transported to the liver and then distributed throughout the body. Zinc is mostly bound to albumin (60–80%) and to a lesser extent to  $\alpha$ -2-macroglobulin and transferrin and taken up by peripheral tissues and the liver where it may be stored as metallothionein. Although 86% is in skeletal muscle, there are certain areas where zinc concentration is especially high and may represent functional importance: they are the prostate, hippocampus, pancreas, and kidney cortex. The highest concentrations of zinc in humans were

found in liver, kidney, pancreas, prostate and eye. Zinc is also present in plasma, erythrocytes and leukocytes. In healthy subjects, the normal plasma zinc concentration is about 1 mg/litre.

### **IV.3 Pharmacodynamics**

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

Zinc is one of the most important trace elements in the body, with three major biological roles; catalytic, structural, and regulatory. It is a multifunctional metal compatible with satisfactory growth, health, and well-being. It is essential for the structure and function of various proteins and cellular components and plays an important role in human physiology from its involvement in the proper function of the immune system to its role in cellular growth, cell proliferation, cell apoptosis, as well as in the activity of numerous zinc-binding proteins.

### **IV.4 Clinical efficacy**

To support the clinical efficacy, the applicant has presented 4 bibliographic reports of studies using intravenous zinc gluconate (Table 1) and 5 studies using intravenous zinc sulfate (Table 2).

The studies using zinc gluconate comprise 3 prospective randomised placebo controlled trials (2 investigating patients with severe burns and one in post elective surgery patients who underwent abdominal aorta reconstruction) and a case series of 4 paediatric patients with severe burns. Wound healing, development of infectious complications including bronchopneumonia, and length of stay in Intensive Care Unit (ICU) were improved in the treated groups.

The studies using zinc sulfate comprise a prospective randomised placebo controlled trial in patients presenting with head injury and 3 open label non-randomised trials (one comparing low with higher dose supplementation in a heterogenous patient population requiring parenteral nutrition, one exploring increasing doses of zinc supplementation in children admitted to intensive care with a risk of mortality or organ failure and one in healthy subjects who were placed on a zinc depleting diet and then treated with intravenous or oral repletion) and an observational study of zinc requirements in patients with long term parenteral nutrition. The studies showed zinc loss was statistically correlated with weight of gastrointestinal loss; low plasma zinc levels normalised on doses of 250 to 750 mcg/kg/day in children, and healthy adults became symptomatically zinc deficient taking 0.23mg/day orally which were corrected by a dose of 66mg/day for 2 days intravenously or 12.2mg/day orally. Patients receiving long term parenteral nutrition at home with trace element supplementation based on serum concentration monitoring received an average dose of  $7.6 \pm 0.74$  mg/day.

Table 1 Bibliographic studies using zinc gluconate

| Author and Design   | Patient population  | Results   |
|---|---|---|
| <b>Placebo Controlled Study</b>   |   |   |
| <b>Faure et al, 1991</b> Prospective randomised parallel placebo controlled trial of 30mg/day vs placebo zinc gluconate day before operation (D-1), immediately post op (D0) and day after operation (D+1). (blinding is not described)   | 30 post-operative elective abdominal aorta reconstruction patients  | No difference between the groups were found on D0; a significant difference was found on D+3, at which time the placebo group serum zinc levels were below D0 levels and the treated group levels were back to normal levels. All complications in wound healing occurred in patients in the placebo group and these patients recorded serum zinc levels that were lower than the mean value of the placebo group.  |
| <b>Berger et al, 1998</b><br>Double blind placebo controlled parallel design study with 1:1 randomisation to supplemented trace elements or standard trace elements plus placebo (40.4 µmol Copper, 2.9 µmol selenium, and 406 µmol (≅26.55mg) zinc as zinc gluconate (group TE) or standard trace element intakes plus placebo (20 µmol copper, 0.4 µmol selenium, and 100 µmol (≅6.5mg) Zn (group C) for 8 days.  | 20 patients with >30% body surface area (BSA) burns   | Mean plasma zinc concentrations decreased significantly more in group C on day 1 than in group TE and remained below the reference range until day 20 in both groups.<br>Pulmonary infections during the first 30 days were apparently reduced although this may have been confounded by an imbalance in inhalation injuries. No difference was found in development of ARDS. The length of stay in the ICU and length of hospital stay were not significantly different between groups. When length of ICU treatment was normalized for burned surface area, the duration was significantly shorter in the supplemented than in control group (P = 0.034). |
| <b>Berger et al, 2007</b><br>Prospective, randomized, placebo-controlled trial. zinc gluconate 37.5 mg, copper gluconate, 3.75 mg and sodium selenite 375 µg intravenously (TE group) or vehicle (V group) for 14–21 d. Blood and urine samples were collected until day 20, and skin biopsy specimens were collected on days 3, 10, and 20. Randomisation was stratified by burned surface (< or ≥50% BSA), inhalation injury confirmed by bronchoscopy (yes or no), and age (< or ≥50 y). | 21 patients with burns >20% of their BSA with ≥10% 2nd intermediate to deep on admission.<br>Controls were 6 healthy subjects undergoing plastic surgery with skin resection. All patients initiated enteral feeding within 16 hrs of admission | There was no significant difference in mean plasma zinc levels between the groups. Zinc concentrations in the placebo group in both burned and healthy skin remained stable over time and did not differ significantly in healthy and burned areas but and were significantly lower than in the treated group by day 20.<br>Supplementation was associated with a significant reduction in infectious complications, especially bronchopneumonia. Wound healing was better in the TE group as shown by the lower grafting requirements  |
| <b>Stucki et al, 2010</b><br>Open label uncontrolled observational case series. A normal saline solution containing copper gluconate, sodium selenite and zinc gluconate was infused. The total daily infused dose of zinc gluconate was between 1.0 and 1.4mg/kg/day for 7 to 15 days. In addition, children admitted to the paediatric ICU received a mixture of vitamin C and vitamin E.   | 4 children aged 3.8, 5, 12 and 15 years with 14 to 53% BSA burns.   | Normalisation of copper, zinc, selenium and glutathione peroxidase plasma concentrations was achieved by day 5 of the ICU stay.   |

**Table 2 bibliographic using another intravenous zinc preparation- zinc sulfate**

| <b>Author and Design</b>   | <b>Patient population</b>   | <b>Results</b>   |
|--|---|--|
| <p><b>Young 1996</b><br/>Randomized, prospective, double-blind 2 period controlled trial of 2.5mg vs 12mg elemental zinc per day (zinc sulfate in TPN or oral zinc gluconate) for 15 days followed by oral 22mg elemental zinc or placebo for 3 months.<br/>(Post interim analysis of the first 14 patients, the intravenous dose of zinc was increased from 8 to 12 mg) The study pharmacist was unblinded.</p>   | <p>68 patients with blunt head injury and brain injury. Initial nutrition was by total parenteral nutrition (TPN) and then weaned to enteral feeding.</p> | <p>One month after injury, the mortality rates in the standard zinc group and the zinc-supplemented group were 26 and 12%, respectively.<br/>It was concluded that zinc supplementation during the immediate post-injury period is associated with improved rate of neurologic recovery and visceral protein concentrations for patients with severe closed head injury.</p>   |
| <p><b>Wolman 1979</b><br/>Prospective 3 period open label uncontrolled trial comparing low and high doses of zinc; one dose daily per period; periods were in a randomised order (0mg, 1.5mg, 3mg vs. 6.0mg, 12.0mg, 23.0mg zinc sulfate)</p>  | <p>24 patients requiring TPN (14 normal controls used to compare with urinary loss of Zinc in patients but no other information provided.)</p>            | <p>In patients with stool and intestinal output <math>\leq 300\text{g/day}</math>, 3mg resulted in positive zinc balance.<br/>In patients with high output small intestinal fluid loss, 12mg/d corrected zinc balance, zinc loss was statistically correlated with weight of GI loss/day.</p>  |
| <p><b>Lowe et al 2004</b><br/>A 3 period parallel group depletion/repletion study. No randomisation is described.<br/>Period 1: 16 day period 12.3mg/day oral zinc<br/>Period 2: 41 day depletion period 0.23mg/day oral zinc;<br/>Period 3: subjects were divided into 2 groups.<br/>Group (A): 2 overnight infusions 66mg/d infusion of zinc sulfate, followed by repletion diet containing 12.2mg/day;<br/>Group (B): dietary repletion alone of 12.2mg/day from day 1.</p> | <p>12 healthy non-smoking male subjects who were rendered zinc depleted by diet in period 2.</p>  | <p>Five subjects completed the 3 month protocol (3 subjects in group A and 2 in group B).<br/>All subjects developed symptoms of zinc deficiency. Two subjects developed symptoms of zinc deficiency requiring intravenous repletion on days 33/34 and 40/41 respectively. All symptoms were rapidly reversed by repletion. Plasma zinc concentration fell 74% during depletion (<math>P &lt; 0.05</math>). Urine zinc concentration followed a similar pattern, falling by 97% during depletion. Both measures returned to baseline values following zinc repletion. Subjects lost <math>39 \pm 9</math> mg of zinc during period 2. During period 3, <math>108 \pm 55</math> mg of zinc was gained, although this was highly variable among subjects, ranging from 30 to 175 mg.</p> |

| Author and Design   | Patient population  | Results  |
|---|---|--|
| <p><b>Cvijanovich et al 2015</b><br/>4 parallel group open label unrandomised pharmacokinetic study of IV Zinc supplementation of paediatric patients admitted to ICU. Patients were sequentially enrolled into 4 dosing groups: (1) no zinc, (2) Zn250: 250 mcg/kg/d ZnSO<sub>4</sub>, (3) Zn500: 500 mcg/kg/d ZnSO<sub>4</sub>, or (4) Zn750: 750 mcg/kg/d ZnSO<sub>4</sub>. ZnSO<sub>4</sub> was administered 3 times daily for 7 days. Plasma Zinc (pZn) was measured at baseline, end of first ZnSO<sub>4</sub> infusion, 1 hour post infusion, and 7 hours post infusion on day 1, then daily through days 2–7. A DSMB assessed the findings in each group before proceeding to recruitment to the next highest dose level group.</p> | <p>24 Children (6 in each group) &lt;10 years old admitted to intensive care unit (ICU) with either unadjusted Paediatric Risk of Mortality III Score &gt;5 or ≥1 organ failure and anticipated stay on paediatric ICU &gt;3 days. Patients also received standard parenteral or enteral nutrition, including standard amounts of zinc.<br/>The age ranges are presented as interquartile ranges per group.</p> | <p>All patients had low baseline pZn levels. pZn increased over the study period in all the supplemented dose groups and pZn increased more rapidly with higher dose. As the ages of the patients in the groups is not clearly presented, it is not possible to fully assess the data in this study with regard to age group.<br/>In aggregate, mean (SD) clearance was 5.77 (2.57) mL/h/kg, volume of distribution was 1.39 (0.46) L/kg, and T<sub>1/2</sub> (half-life) was 181.36 (56.29) hours.<br/>Based on pharmacokinetic modelling, the 500-mcg/kg/d IV zinc supplementation dose nearly restored levels to within the normal range, without inducing prolonged periods of pZn above normal. No patient had a study-related adverse event.</p> |
| <p><b>Btaiche et al 2011</b><br/>A retrospective observational study to evaluate parenteral trace element dosing, serum concentrations, frequency of monitoring patients having parenteral nutrition at home and exploring the relationship between</p>   | <p>26 adult and adolescent patients &gt;40kg requiring long term parenteral nutrition at home for &gt;1 year</p>  | <p>An average zinc dose in parenteral nutrition of 7.6 mg/day (about 9 mg/day in patients with short bowel syndrome as compared to 6.7 mg/day for non-short bowel syndrome patients, p=0.12) maintained normal serum zinc concentrations within the reference range in the majority (90%) of cases</p>   |

**Supplementation in parenteral nutrition:**

Deficiencies in zinc are frequent in patients for whom Parenteral Nutrition (PN) is indicated. Recent publications indicate the recommended amounts for basal requirements depending on the patient age. It should be noted that an additional supplementation can be used in specific pathologic situations.

**Table 2: Current recommended daily oral and parenteral zinc requirements**

| Population   | Adults<br>Parenteral doses<br><i>Oral doses</i>                                  | Children<br>Parenteral doses<br><i>Oral doses</i>  | Infants<br>Parenteral doses<br><i>Oral doses</i>  | Prematures<br>Parenteral doses<br><i>Oral doses</i> |
|--------------|--|--|---|---|
| ASPEN 2012   | 2.5-5 mg*<br><br><i>M 11 mg, F 8 mg<br/>Pregnant: 11 mg<br/>Lactation: 12 mg</i> | 50 µg/kg/d<br>(max 5000 µg/d)<br><br><i>4-8 y: 5 mg<br/>9-13 y: 8 mg<br/>14-18 y: M: 11 mg<br/>F: 9 mg</i> | <3 mo: 250 µg/kg/d<br>>3 mo: 50 µg/kg/d<br>(max 5000 µg/d)<br><br><i>0-6 mo: 2 mg<br/>7 mo-3 y : 3 mg</i> | 400–500 µg/kg/d<br><br><i>1000-3000 µg</i>          |
| ESPGHAN 2005 |  | 50 µg/kg/d (up to a maximum of 5 mg/d)   | < 3mo: 250µg/kg/d<br>>3 mo: 100µg/kg/d  | 450-500 µg/kg/day                                   |

\*Same value indicated in the ESPEN guideline [Brage 2009]

**Table 3: Zinc content in parenteral Multi-TE products available in Europe  
(from ASPEN 2012 Table 13)**

| Products (distributor)*                          | Zinc content<br>mg (µmol) | Volume |
|--|---------------------------|--------|
| <b>Adults</b>                                    |                           |        |
| Additrac (Fresenius Kabi)                        | 6.5 (99.4)                | 10 ml  |
| Decan (Baxter & Laboratoires Aguettant)          | 10 (153)                  | 40 ml  |
| Tracutil (B. Braun)                              | 3.3 (50)                  | 10 ml  |
| <b>Pediatrics and Neonates</b>                   |                           |        |
| Peditrace (Fresenius Kabi)                       | 0.25 (3.82)               | 10 ml  |
| Inzolen-Infantibus sine NaK (Kohler)             | 0.097 (1.49)              | 10 ml  |
| Oligo-elements Aguettant Pediatrique (Aguettant) | 0.1 (1.53)                | 10 ml  |

\*Information based on manufacturer's information. The content of other TE are not indicated in this table in this table (Copper, Chromium, Manganese, Selenium, Molybdenium, Iron, Iodide, Fluorine and Cobalt)

In adult preparation, the highest Zinc concentration is of 0.65mg/ml (Additrac). In children preparations, the highest Zinc concentration is of 0.25mg/ml (Peditrace).

In patients who receive home PN, deficits have been shown to occur in the absence of substitution, and they can be completely or partially corrected with standard supplies. In the case of total PN, a consensus exists that micronutrients/antioxidants should be supplemented on a daily basis.

One retrospective observational study based on medical record review is presented describing real life use of trace element supplementation for 26 patients receiving long term home based parenteral nutrition. The results showed an average zinc dose in parenteral nutrition of  $7.6 \pm 0.74$  mg/day maintained normal serum zinc concentrations within the reference range in the majority (90%) of cases.

**Situations where a pronounced deficiency may occur:**

Additional bibliographic studies are supplied to support this indication which is in line with the only currently approved intravenous zinc gluconate product in the EU (ZINC INJECTABLE à 1 mg/ml).

Severe Malnutrition

A study in which healthy volunteers were rendered zinc depleted by diet and then treated with zinc infusion plus oral repletion or oral repletion alone showed efficacy in dietary repletion as would be seen in malnutrition.

Hypercatabolism

Studies are presented which support supplementation of zinc in patients who are in catabolic states post-surgery or severe burn which appear to show better wound healing or reduced complications due to infections or with wounds, or reduced length of stay in intensive care. It appears to be recognised that zinc is required to support the wound healing process and there is some evidence provided to show that wounds in patients have higher levels of zinc than healthy skin in the same patient.

An additional study is presented that is supportive. Three doses of 30mg/day zinc gluconate pre- and post-operatively was used in a prospective randomised placebo controlled parallel design trial in 30 post-operative elective abdominal aorta reconstruction patients. Serum zinc levels were shown to be higher in the treated group and observation of the surgical wounds after surgery revealed that all who experienced healing complications were in the placebo group.

Digestive fistula and diarrhoea

Studies are presented which support supplementation of zinc in patients who are at risk of negative zinc balance due to gastrointestinal losses.

A study measuring zinc balance in patients with conditions that may be considered to have a risk of increased zinc loss showed a correlation between zinc loss and zinc balance. Negative zinc balance was only addressed by patients who had zinc supplements greater than the measured loss via intestine and urine.

**Dosage requirements**Adult

The presented studies use elemental doses of zinc from 23 to 30mg/day. The only presented study in long term parenteral nutrition found that the average dose of zinc was  $7.6 \pm 0.74$  mg/day (about 9 mg/day in patients with short bowel syndrome as compared to 6.7 mg/day for non-short bowel syndrome patients).

In patients recognised to have conditions expected to be associated with higher zinc requirements (burns or post major surgery) or zinc loss (due to gastrointestinal loss), the presented studies used doses ranging from 23mg/day to 37.5mg/day and a study in healthy volunteers which was designed to render the subjects zinc deficient used a dose of 66mg/day for 2 days to replenish zinc balance.

Academic groups have published guidelines which suggest 2.5-5mg/day supplementation to address basal requirements with increases to 30-35mg/day in patients with severe burns and a pragmatic approach to correct zinc balance based on observed losses via gastrointestinal route of 12-17mg/litre of GI loss/day; however no clear supportive data is provided for these doses.

Paediatric

The applicant requests that the dose for children is exactly that recommended in the Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and

Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR) 2005 for premature babies, infants and children. The applicant suggests that the currently approved text in the approved product in France follows older guidelines.

A case series using zinc gluconate in patients aged 8 to 15 with severe burns used doses of 1.0 to 1.4mg/kg/day and stated that normalisation of plasma concentrations was achieved by day 5 of the ICU stay. A dose finding study in 24 children found that 4/6 of the group dosed with 750mcg/kg/day achieved supratherapeutic levels of plasma zinc (>120mcg/dL) and the authors concluded that, although the dose appeared well tolerated, the maximum dose of 500mcg/kg/day was appropriate as this dose nearly restored levels to within the normal range without inducing periods of plasma zinc concentrations above normal. The ages of the children were presented as the interquartile ranges of each group, thus it is not possible to assess the impact of age on dose.

Based on the provided bibliographic evidence, current EU and US academic group published guidelines and taking into account the currently approved product in France and the CMS Day 145 comments, the proposed posology is

Adults:

- 2.5 to 5 mg/day

Paediatric population:

- premature: 0.45 to 0.50 mg/kg /day

- infants younger than 3 months: 0.25 mg/kg /day

- infants older than 3 months: 0.10 mg/kg /day

- children: 0.05 mg/kg/day to a maximum of 5 mg/day.

### **Conclusion of Clinical Efficacy**

The proposed indication and posology are supported by the submitted data.

ESPEN guidelines state that zinc levels should be monitored and adjusted accordingly in long term parenteral nutrition. In conditions of increased zinc loss or increased zinc requirements, parenteral zinc supplementation is advised due to competition with copper in intestinal absorption of oral zinc.

The applicant has presented data to support supplementation with zinc parenterally in situations of high GI loss or increased zinc requirements (for example in burns or wound healing) and higher doses than those required to meet basal daily requirements may be appropriate in these situations.

The proposed wording of section 4.2 of the SmPC reflects that the dosage must be adjusted for each patient, taking into account losses and zinc status and that higher doses than those required for daily basal requirements may be required to compensate for zinc losses.

### **IV.5 Clinical Safety**

There have been no reports of adverse events in patients taking zinc gluconate at the recommended doses and most of the presented bibliographic studies are historical, without presentation of safety data in the publication. One published study changed administration from peripheral to central venous access due to a subjective impression from nursing staff that there was a degree of phlebitis when zinc sulfate was infused peripherally. In addition, the Marketing Authorisation Holder (MAH) for ZINC INJECTABLE à 1 mg/ml, the only currently authorised zinc gluconate product in the EU, reports that 6 out of the 14 reports on its safety database concern infusion site inflammation. Therefore it is appropriate to include infusion site inflammation as an adverse drug reaction in section 4.8 of the SmPC.

A cumulative summary of safety from the MAH for ZINC INJECTABLE à 1 mg/ml reports 14 cases on the safety database which has been marketed since 1986 with an estimated patient exposure globally of 4,668,810. No other safety signals have been identified from the reports.

With regard to unintentional medication errors, 3 reports of oral administration have been received.

Reports of overdose of intravenous zinc solutions have been published, but again, these are very few and report hyperamylasaemia without evidence of acute pancreatitis, nausea, vomiting, fever, anaemia, hypotension, pulmonary oedema, diarrhoea, jaundice, oliguria, cardiac arrhythmias and thrombocytopenia.

Therefore it is appropriate to include these observed effects in overdose in section 4.9 of the SmPC.

### **Conclusions on clinical safety**

There have been no reports of adverse events in patients taking zinc gluconate at the recommended doses and most of the presented bibliographic studies are historical, without formal presentation of safety data.

There is sufficient evidence to list infusion site inflammation as an adverse drug reaction in section 4.8 of the SmPC.

The overdose in section 4.9 of the SmPC adequately describes the associated adverse events that might be observed based on reports of overdose.

### **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 Zing 1 mg/ml concentrate for solution for infusion.

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

| <b>Safety concern</b>   | <b>Important identified risk: Hypersensitivity</b>  |
|---|---|
| Objective(s) of the risk minimisation measures  | Description of the risk   |
| Routine risk minimisation measures  | (Proposed) text in SmPC<br>Section 4.3: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. |
|   | Comment: none   |
|   | Other routine risk minimisation measures: none  |
| Additional risk minimisation measure(s)<br>(repeat as necessary)                        | None proposed   |
| <b>Effectiveness of risk minimisation measures</b>                                      |   |
| How effectiveness of risk minimisation measures for the safety concern will be measured | Quarterly signal detection  |
| Criteria for judging the success of the proposed risk minimisation measures             | Monitoring of frequency of occurrence   |
| Planned dates for assessment  | Quarterly   |
| Results of effectiveness measurement  | Not applicable  |
| Impact of risk minimisation   | Not applicable  |
| Comment   | None  |

| <b>Safety concern</b>                          | <b>Important identified risk: Overdose</b>   |
|--|--|
| Objective(s) of the risk minimisation measures | Description of the risk  |
| Routine risk minimisation measures             | (Proposed) text in SmPC<br>Section 4.9: Hyperamylasaemia without evidence of acute pancreatitis, nausea, vomiting, fever, anaemia, hypotension, pulmonary oedema, diarrhoea, jaundice, oliguria, cardiac arrhythmias and thrombocytopenia have been reported in patients with overdose. Other manifestations of toxicity may include profuse sweating, blurred vision, decreased consciousness and hypothermia |
|  | Comment: none  |
|  | Other routine risk minimisation measures: none   |

|   |  |
|---|--|
| <b>Safety concern</b>   | <b>Important identified risk: Overdose</b> |
| Additional risk minimisation measure(s)<br>(repeat as necessary)                        | None proposed                              |
| <b>Effectiveness of risk minimisation measures</b>                                      |  |
| How effectiveness of risk minimisation measures for the safety concern will be measured | Quarterly signal detection                 |
| Criteria for judging the success of the proposed risk minimisation measures             | Monitoring of frequency of occurrence      |
| Planned dates for assessment  | Quarterly                                  |
| Results of effectiveness measurement  | Not applicable                             |
| Impact of risk minimisation   | Not applicable                             |
| Comment   | None                                       |

|   |   |
|---|---|
| <b>Safety concern</b>   | <b>Important potential risk: Zinc induced copper deficiency</b>   |
| Objective(s) of the risk minimisation measures  | Assessment of clinical impact of this interaction   |
| Routine risk minimisation measures  | (Proposed) text in SmPC:<br>Section 4.5: Large doses of oral zinc inhibit copper absorption. Clinical significance of this interaction for intravenous zinc remains unclear |
|   | Comment: none   |
|   | Other routine risk minimisation measures: none  |
| Additional risk minimisation measure(s)<br>(repeat as necessary)                        | None proposed   |
| <b>Effectiveness of risk minimisation measures</b>                                      |   |
| How effectiveness of risk minimisation measures for the safety concern will be measured | Quarterly signal detection  |
| Criteria for judging the success of the proposed risk minimisation measures             | Monitoring of frequency of occurrence   |
| Planned dates for assessment  | Quarterly   |
| Results of effectiveness measurement  | Not applicable  |
| Impact of risk minimisation   | Not applicable  |
| Comment   | None  |

#### **IV.7 Discussion of the clinical aspects**

It is recommended that a Marketing Authorisation is granted for Zinc 1 mg/ml, 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 AND BENEFIT-RISK ASSESSMENT**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with zinc gluconate is considered to have demonstrated the therapeutic value of the compound. 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 |
|--------------|----------------------|------------------------------|--------------------------------|--------------------------|------------------------|
| RMS-Transfer | UK/H/5571/001/<br>DC | No                           | 16.04.2018                     | 16.04.2018               | Approved               |