Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Selenium 10 micrograms/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 10 ml solution contains 219 micrograms of sodium selenite, equivalent to 100 micrograms of selenium.

Each ml of solution contains 21.9 micrograms of sodium selenite, equivalent to 10 micrograms of selenium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear colourless solution.
pH 8.0 – 9.5
Osmolarity = 20 mOsm/l

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention of selenium deficiency in patients receiving parenteral nutrition.
Treatment of proven selenium deficiency that cannot be compensated by nutrition alone.

4.2 Posology and method of administration

Posology

1 ml of solution contains 10 micrograms of selenium.

The dose must be adapted individually according to selenium deficiency and selenium status.
For monitoring of therapy the selenium concentration in whole blood or serum should be determined. In long term parenteral nutrition, control of blood levels should be performed at 6-12 months intervals, except if clinical symptoms of a deficiency are suspected.
Adults:
Plasma selenium concentrations from 80 to 120 µ/L (in whole blood: 100 to 140 µg/l) have been proposed to be adequate in adults. At levels above the normal selenium levels, the dose should be reduced.

Pediatric population:
Age specific reference values for normal selenium concentrations apply for monitoring of therapy.

The recommended posology is:

- Adults:
  - Supplementation to total parenteral nutrition: 60 to 100 micrograms daily.
  - Other situation with proven selenium deficiency: 100 micrograms up to a maximum of 400 micrograms daily for a short-term until normalization of laboratory monitoring values.
- Paediatric population:
  - Infants: 2 micrograms/kg/day and infants with low birth weight: 2 to 3 micrograms/kg/day.
  - Children: 2 micrograms/kg/day, up to a maximum of 30 micrograms daily.

Method of administration
Intravenous administration:
Selenium 10 micrograms/ml concentrate for solution for infusion must be administered after dilution in solution for parenteral nutrition, after stability has been validated, or in isotonic solution (such as sodium chloride 0.9% or glucose 5%) with a slow infusion rate.

4.3 Contraindications

This product must not be administrated in case of selenium poisoning or hypersensitivity to selenium containing products.

4.4 Special warnings and precautions for use

Special warnings:
The product must not be injected straight, but diluted in a solution for infusion (see section 4.2).

Precautions for use:
Serum selenium levels must be controlled regularly.

In case of complex parenteral nutrition and if mixing of medicines is necessary, caution is required in order to avoid incompatibilities.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Selenium in pregnant women. Limited published data from animal studies reveal only evidence for toxicity to reproduction at maternally toxic doses (see section 5.3.). No adverse effect of sodium selenite on the pregnancy or unborn child is expected, provided that it is used in case of proven selenium deficiency.

Lactation
Selenium is excreted in human milk, but at therapeutic doses of selenium no effects on the breastfed newborns/infants are anticipated. Selenium can be used during breast-feeding.

Fertility
There are no data on fertility from the use of selenium in humans. Selenium did not impair male fertility in rats, and effects of selenium on female fertility in rodents were only observed at very high doses (see section 5.3). Overall, doses used to correct selenium deficiency are not expected to exert adverse effects on fertility.

4.7 Effects on ability to drive and use machines

SELENIUM 10 micrograms/ml concentrate for solution for infusion has no influence on the ability to drive and use machines.

4.8 Undesirable effects

No adverse effects are observed in normal conditions of use.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971;

Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie

4.9 Overdose

Symptoms of acute overdose are: garlicky breath, tiredness, nausea and vomiting, diarrhoea and abdominal pain. In case of chronic overdose, effects on skin and skin appendages with changes in the nail and hair growth as well as peripheral polyneuropathies have been observed.
In case of overdose, the treatment must be interrupted, and a symptomatic treatment should be given if necessary. In case of acute overdose by ingestion of large amount of selenium, gastric lavage and forced diuresis are possible. In case of extreme overdose (1,000 – 10,000x), elimination of selenite by dialysis can be attempted. There is no known specific antidote. In case of intoxication, selenium blood levels should be controlled at least once a month, until return to a level conform to the recommendations.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mineral supplements.
ATC code: A12CE02

Selenium is an essential trace element. Up to 20 selenoproteins have been identified in rodents. In human, selenium compounds are glutathione peroxidase and a selenium protein P found in the plasma. In both these proteins, selenium is protein-bound and is present in the form of the amino acid selenocysteine. Other selenium-dependent enzymes are the thioredoxine-reductase and the 5'-deiodinase that catalyses the conversion from tetraiodothyronine (T4) to the active thyroid hormone triiodothyronine (T3).

The selenium-containing glutathionperoxidase is a part of the anti-oxidative protection system of the mammal cell. In case of sufficient quantities of reduced glutathione, the glutathionperoxidase converts a variety of hydroperoxides into relevant alcohols. In cellular or sub-cellular in vitro models, it has been observed that the integrity of cellular or sub-cellular membranes depends on the intactness of the glutathionperoxidase system. Synergetic effect with vitamin E in various cell fractions is postulated but has not been conclusively proven. Selenium as a part of the glutathionperoxidase can reduce the lipidperoxide rate and the resulting membrane damage.

The patho-physiological relevance of selenium-dependent reactions has been demonstrated by observations in selenium deficiency humans and animals. The selenium-containing glutathionperoxidase affects the leucotriene, thromboxane and prostacyclin metabolism. Selenium deficiency inhibits reactions of the immune system, especially the non-specific, cell-bound and humoral reactions. Selenium deficiency affects the activity of a few liver enzymes. Selenium deficiency potentiates oxidatively or chemically induced liver damage and toxicity of heavy metals such as quicksilver and cadmium.

Deficiency of selenium has been associated with an endemic form of cardiomyopathy, Keshan disease. It has also been associated with Kaschin-Beck disease, an endemic osteoarthropathy which causes a severe deformity of the joints.
Clinically manifested selenium deficiency has also been seen to be a result of long-term parenteral nutrition and unbalanced diets. Cardiomyopathies and myopathies are observed most frequently.

5.2 Pharmacokinetic properties

In the blood, selenite is mainly absorbed by erythrocytes and enzymatically reduced to hydrogen selenide. Hydrogen selenide serves as the central selenium pool for excretion and for specific incorporation in selenoproteins. In this reduced form, selenium is bound to plasma proteins present in the liver and other organs. The plasmatic secondary transport from the liver to the glutathionperoxidase-synthesing target tissues takes place in the form of selenocystein (selenoprotein P). The further metabolic process of the selenoprotein biosynthesis is currently known only in prokaryotes. Selenocystein is then specifically incorporated into the peptide chains of the glutathionperoxidase.

Excess of hydrogen selenide is transformed into methylated metabolites (methyl selenol, dimethylselenide and trimethylselenonium ion) prior to being excreted into urine and/or exhaled.

The total quantity of selenium in the human body is between 3 mg and 20 mg. In human, selenium is excreted in feces, urine or lung, depending on the administered dosage. Selenium is primarily renally excreted in the form of trimethylselenonium ion. The excretion depends on the selenium status.

The selenium excretion after the intravenous or oral intake takes place in three phases with a terminal half-life of 65 to 116 days.

5.3 Preclinical safety data

Published literature on single and repeated dose toxicity of selenium and sodium selenite reveals no evidence for adverse health effects in addition to those already known from experience in humans. Toxicity to reproduction was only found at very high doses and no evidence was found for a risk of teratogenic effects in mammals at non-maternally toxic doses. Although mutagenicity and carcinogenicity data are inconclusive, because there is evidence for both positive as well as negative effects, the adverse effects on these endpoints are generally found at concentrations above the normal physiological levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection.

6.2 Incompatibilities

Selenium is generally incompatible with high concentration of ascorbic acid (reduction of selenite to elemental selenium which is not soluble and unavailable as a nutritional source of selenium).
SELENIUM 10 micrograms/ml concentrate for solution for infusion can not be mixed with medicines except those mentionned in section 6.6

6.3 Shelf life

3 years.
After dilution, chemical and physical in-use stability has been demonstrated for 48 h at 25°C.

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

6.4 Special precautions for storage

There are no special storage conditions.

6.5 Nature and contents of container

10 ml solution in a type I glass vial with a type I elastomer (bromobutyl) stopper fitted with an aluminium cover and crimped.
Pack of 10 vials.

6.6 Special precautions for disposal

SELENIUM 10 micrograms/ml concentrate for solution for infusion can not be mixed with medicines other than sodium chloride 0.9%, glucose 5%, solution for parenteral nutrition or solution of trace elements.
Each ml of concentrate should be diluted in at least 5 ml of solution for infusion.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoire AGUETTANT
1, rue Alexander Fleming
69007 LYON
France

8 MARKETING AUTHORISATION NUMBER

PA1968/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 4th March 2016

10 DATE OF REVISION OF THE TEXT

March 2017