Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Selesyn 100 micrograms/2 ml, oral solution (50 micrograms/ml)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 2 ml oral solution contains 100 micrograms selenium in the form of 333 micrograms sodium selenite pentahydrate ($Na_2SeO_3 \cdot 5\ H_2O$), corresponding to 50 µg/ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.
Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Proven selenium deficiency that cannot be offset from food sources.

4.2 Posology and method of administration

Posology
100–200 micrograms selenium (equivalent to 1-2 ampoules). If more selenium is necessary to reach the normal blood level, this dose can be increased to 500 micrograms selenium (equivalent to 5 ampoules = 5 x 100 micrograms or 1 drinking bottle = 500 micrograms, respectively).

Paediatric population
2 µg/kg body weight/day at therapy onset and a maintenance dose of 1 µg/kg body weight/day.

For measuring a children's dose of less than 1 ml oral solution approximately 5 ml oral solution is placed in the measuring cup and the needed volume is drawn up with the enclosed pipette. For example for a 1-year-old child with 10 kg body weight the maintenance dose is 10 µg per day corresponding to 0.2 ml oral solution.

Selenium levels in whole blood or serum should be determined in order to monitor the success of therapy.

Maximum daily doses for children for a longer time:

Age (years)	UL (µg selenium/day)
1-3	60
4-6	90
7-10	130
11-14	200
15-17	250

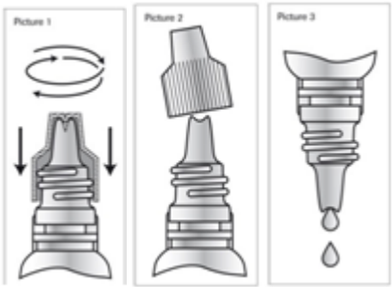
Dosage in patients with renal or hepatic impairment
There is no scientific evidence on dosage adjustment in patients with renal or hepatic impairment.

Method of administration

Detach a single-dose ampoule from the remainder of the strip of ampoules and open the oral ampoule by twisting the

top. Squeeze out the whole of the contents of the ampoule into the mouth.

In the case of the drinking bottles:



Picture 1:
Before use the drinking bottle has to be made ready for use. For opening the screw cap is first turned clockwise down in order to open the drinking bottle with the integrated spike of the screw cap.
Picture 2:
Then the screw cap is turned off anti-clockwise.
Picture 3:
The complete contents is placed in the mouth or the required dose is removed by carefully squeezing of the drinking bottle into the enclosed measuring cup with milliliter graduation. Then the drinking bottle is closed firmly.

Hold the liquid in the mouth for about 30–60 seconds before swallowing.

Selenium levels in whole blood or serum should be determined in order to monitor the success of treatment.

There is no time limit to the administration of selesyn® oral solution in a supplementary dose (100 micrograms selenium per day is equivalent to 1 ampoule).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Selenosis.

4.4 Special warnings and precautions for use

None.

4.5 Interaction with other medicinal products and other forms of interaction

It must be ensured that selesyn® oral solution is not administered orally at the same time as reducing substances (e.g. vitamin C), as precipitation of elemental selenium cannot be excluded (see section 6.2 "Incompatibilities").

Elemental selenium is not soluble in an aqueous medium and has no biological availability. Oral administration of selesyn® oral solution and vitamin C should be given at an interval of 4 hours.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of selesyn® in pregnant woman. Limited published data from animal studies reveal only evidence for toxicity to reproduction at maternally toxic dose.

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.

Breastfeeding
Selenium is excreted in breast milk. Doses correcting selenium deficiency in breast feeding woman are not expected to exert adverse effects on the suckling infant.

Fertility
There are no data available regarding the effect on fertility.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

None known to date when selesyn® oral solution is used as directed.

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
E-mail: medsafety@hpra.ie

4.9 Overdose

Signs of an acute overdose are an odour of garlic on the breath, tiredness, nausea, diarrhoea and abdominal pain. Chronic overdose can affect growth of nails and hair and may lead to peripheral polyneuropathy.

Countermeasures include gastric lavage, forced diuresis or the administration of high doses of vitamin C. In the case of an extreme overdose (1,000–10,000 times the normal dose) an attempt should be made to eliminate the selenium by dialysis. Administration of dimercaprol is not recommended as the toxic effect of selenium is potentiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mineral supplement
ATC code: A12C E02

Selenium is a co-factor in various enzymes in the human body and therefore belongs to the essential trace elements. To date, more than 25 proteins and protein subunits containing selenium have been identified and most clinical and biochemical effects of selenium can be attributed to their activity. However, not all the effects of selenium are exclusively related to the action of different enzymes.

Selenium-containing glutathione peroxidase and selenium protein P have been identified in humans. Glutathione peroxidase is part of the anti-oxidant protection mechanism of the cell in mammals. As a constituent of glutathione peroxidase, selenium can delay the lipid peroxidation rate and thus the resultant damage to the cell wall. Glutathione peroxidase affects the metabolism of leukotrienes, thromboxanes and prostacyclines. In animals, type I iodothyronine-

5'-deiodinase is characterised as a selenium enzyme that converts thyroxine (T_4) into triiodothyronine (T_3), the active thyroid hormone.

A selenium deficiency is manifested in reduced selenium levels in whole blood or plasma and in the suppression of glutathione peroxidase activity in whole blood, plasma or thrombocytes. The pathophysiological relevance of selenium-dependent reactions has been demonstrated in studies of selenium deficiencies in humans and animals: Selenium deficiency activates and inhibits the response of immunological mechanisms, particularly non-specific cell and body fluid responses. Selenium deficiency affects the activity of various hepatic enzymes. Selenium deficiency potentiates damage occasioned to the liver by oxidative or chemical factors and the toxicity of heavy metals such as mercury and cadmium.

For humans, the following diseases are described as a consequence of selenium deficiency: Keshan disease, an endemic cardiopathy, and Kaschin-Beck disease, an endemic osteoarthropathy that is associated with very severe deformity of the joints. Clinically manifest selenium deficiency is also observed as a consequence of long-term parenteral nutrition and unbalanced diets.

5.2 Pharmacokinetic properties

Sodium selenite is not immediately converted to proteins. In the blood, the majority of the supply of selenium is used by the erythrocytes and converted to hydrogen selenide under the action of enzymes. Hydrogen selenide acts as a central pool of selenium for both elimination and the specific integration of selenium in selenoproteins. Reduced selenium binds to plasma proteins that migrate to the liver and other organs. Secondary plasma transport from the liver to the target tissues, that produce glutathione peroxidase by synthesis, probably occurs via a P-selenoprotein containing selenocysteine. The subsequent metabolic pathway of selenoprotein synthesis has to date only been studied in prokaryotes. In the metabolic process, selenocysteine is specifically incorporated in the peptide chains of glutathione peroxidase.

All excess hydrogen selenide is metabolised via methylselenol and dimethylselenide to the trimethylselenonium ion, the principal elimination product.

After oral administration, selenium is principally absorbed from the small intestine. Absorption of sodium selenite in the intestine is not regulated by homeostatic mechanisms. Depending on the concentration of sodium selenite and the presence of related substances, it is usually between 44% and 89%, and sometimes more than 90%. The amino acid cysteine increases the absorption of sodium selenite.

The total quantity of selenium present in the human body is between 4 mg and 20 mg. Humans excrete selenium in the faeces, via the kidneys and through the respiratory system, depending on the amount administered. Selenium is predominantly eliminated in the form of the trimethylselenonium ion via the kidneys. Elimination is dependent on the selenium status.

After intravenous or oral administration, the process of selenium elimination was divided into three phases. After oral administration of 10 micrograms in the form of [^{75}Se] sodium selenite, 14–20% of the absorbed selenium is eliminated via the kidneys in the first two weeks, while almost nothing was eliminated via the lungs and skin. The retention of selenium in the whole body decreased in three phases, with half-lives of 0.7–1.2 days in phase 1, 7–11 days in phase 2 and 96–144 days in phase three. The selenium concentration decreased more rapidly in the liver, heart and plasma than in the joint muscles or in the bones. Of an intravenously administered dose of [^{75}Se] sodium selenite, 12% was excreted in the first 24 hours. A further 40% was eliminated with a biological half-life of 20 days. The half-life of the third phase was 115 days.

Elimination after oral and intravenous administration of a physiological dose of [^{74}Se] sodium selenite was compared directly: after administration of 82 micrograms selenium in the form of sodium selenite, 18% of the intravenous dose and 12% of the oral dose was eliminated via the kidneys in the first 24 hours together with metabolised physiological selenium. After this phase, the process of elimination by both routes of administration is more or less the same. In healthy volunteers, the elimination of orally and parenterally administered sodium selenite was comparable.

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 ef-fects 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

Sodium chloride
Hydrochloric acid
Water for injections.

6.2 Incompatibilities

When preparing an oral solution with Selesyn as a supplement, it must be ensured that the pH value does not fall below 7.0 and that the solution is not mixed with reducing substances (e.g. vitamin C), as a precipitate of elemental selenium may possibly result. Elemental selenium is not soluble in an aqueous medium and has no biological availability. Oral administration of Selesyn and vitamin C should be given at an interval of 4 hours.

6.3 Shelf life

Unopened: 2 years.
Use immediately after opening. Discard any unused contents.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Ampoules each containing 2 ml of oral solution are made of plastic (LDPE).
Pack sizes: 10, 20, 50, 60, 90 and 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

biosyn Arzneimittel GmbH
Schorndorfer Strasse. 32
70734 Fellbach
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1131/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2006

Date of last renewal: 01 November 2008

10 DATE OF REVISION OF THE TEXT

October 2014