selenase®
a chance for your intensive care patients

very well tolerated
modulates inflammatory and coagulation pathways
protects from endothelial and organ damage
reduces mortality
Sepsis patients have low selenium levels


Serum reference range: 74–190 µg/l

1 µmol Se = 78.96 µg Se

Vitoux

379–54.5 µg/l

15.6–73.3 µg/l

10.0–83.0 µg/l

Zimmermann

Serum reference range:

Angstwurm

Sepsis patients have low selenium levels

The more severe the sepsis, the lower the selenium level

Vitoux et al. 1996.
The lower the selenium level, the higher the mortality

Vitoux et al. 1996.
selenase® administration improves prognosis
SIC* study 2005: 28-day mortality

Intention-to-treat analysis, data on file

Per-protocol group data on file

*selenase® in Intensive Care
**SIC* study 2005: Duration of survival according to Kaplan-Meier**

*(preliminary analysis)*

Intention-to-treat analysis, data on file

Per-protocol group data on file

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**selenase® prolongs the duration of survival**

*selenase® in Intensive Care*
Pathophysiology of SIRS/Sepsis

Invasion of bacteria and toxins

**NF-κB Central mediator**

- **Monocytes/macrophages**
  - Neutrophil granulocytes
  - Cytokines: TNF-α, IL-1, IL-6, IL-8

- **Activation of complement**
  - Activated complement products: C3a, C5a

- **Activation of coagulation**
  - Thrombin → fibrin → fibrinolysis
  - PAI-1 inhibits

- **Lipid mediators**
  - Prostaglandins, leukotrienes
  - Thromboxanes, platelet activating factor

- **Proteases**
  - Elastase, collagenase
  - Cathepsin

- **Cytokines**

- **ROS**
  - ‘OH, O₂⁻

- **Adhesion**
  - Endothelium

- **Endothelium**
  - Capillary leakage → permeation into tissues

- **Organ damage** → organ failure → death
**Selenite** reduces complement activation.
(Hou 1997)

**Selenium** is essential for the immune system, acts as an immune modulator (antioxidant and anti-inflammatory).
(Ferencik und Ebringer 2003; Rovensky et al. 2002)

**Selenite** as well as GPX 1, 2, 3, 4 and TR reduce peroxides and regulate the cellular redox state. Oxidative stress induces the expression of GPX and TR.
(McKenzie et al. 2002)

The presence of selenium and thus an adequate GPX 3 and GPX 4 activity inhibits thromboxane synthesis in favor of prostacyclin synthesis: vasodilation ↑ coagulation ↓
(Brigelius-Flohé et al. 2003)

Selenite inhibits TNFα induced expression of endothelial adhesion molecules (ICAM-1, VCAM-1, E-selectin, P-selectin).
(Zhang et al. 2002, Horvathova et al. 1999)

TR stabilize glucocorticoid receptors  → better glucocorticoid response.
(Grippo et al. 1985)

Selenium stimulates the insulin signalling cascade, it has an insulin-like effect  → improved control of glucose levels.
Why high-dose selenium?

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose</th>
<th>RR (random) 95 % CI</th>
<th>relative risk (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berger 1998</td>
<td>Day 0–8: 159 µg Se (+ 40.4 µmol Cu + 406 µmol Zn)</td>
<td></td>
<td>3.00</td>
</tr>
<tr>
<td>Porter 1999</td>
<td>Day 0–7: 50 µg Se (+ 400 IE Vit E + 100 mg Vit. C + 8 g NAC)</td>
<td>impossible to estimate</td>
<td></td>
</tr>
<tr>
<td>Berger 2002</td>
<td>Day 1–14 or 21: 380 µg Se (+ 59 µmol Cu + 574 µmol Zn)</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Berger 2001 a</td>
<td>Day 1–5: 500 µg Se/day</td>
<td></td>
<td>2.67</td>
</tr>
<tr>
<td>Berger 2001 b</td>
<td>Day 1–5: 500 µg Se/day (+ 150 mg Vit. E + 13 mg Zn)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Kuklinski 1991</td>
<td>500 µg Se/day</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Angstwurm 1999</td>
<td>Day 1–3: 535 µg Se; day 4–6: 285 µg Se; Day 7–9: 155 µg Se</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Zimmermann 1997</td>
<td>Day 1: 2000 µg Se; day 2–28: 1000 µg Se</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95 % CI)</strong></td>
<td><strong>Day 0–8: 159 µg Se + 40.4 µmol Cu + 406 µmol Zn</strong></td>
<td><strong>favours selenium</strong></td>
<td><strong>0.59</strong></td>
</tr>
</tbody>
</table>

Heyland et al. 2005

Highest selenium dose – best outcome
Selenium safety

Reference range whole blood selenium levels
1.1–2.9 µmol/l

First symptoms of toxicity from approx. 13 µmol/l = approx. 1000 µg/l

Intake:
- 50–100 µg/d
- 100–1000 µg/d
- 1000–2000 µg/d

1 µmol Se = 78.96 µg Se

Tolerability of selenium/selenase®

Selenium intake (healthy)

- 400–800 µg/day = maximum chronic intake (years)
- 1,000–7,000 µg/day = with chronic intake first reversible symptoms of toxicity
- 70,000–350,000 µg = lethal as a single dose

Literature at biosyn
Selenium metabolism (simplified)

**Organic selenium**
- Selenomethionine (yeast)
- Absorption (as methionine)

**INTERMEDIATE METABOLISM**
- Selenomethionine
- Selenocysteine
- \( \text{H}_2\text{Se}^{(-II)} \) (Hydrogen selenide)

**Specific incorporation into selenoproteins**
- Such as glutathione peroxidases, selenoprotein P, thioredoxin reductases, iodothyronine deiodases and other specific selenoproteins (e.g. in prostate, nuclei, granulocytes, T-cells etc.)

**Inorganic selenium**
- Sodium selenite \( \text{Se}^{(+IV)} \)
  - Reduction by free radicals \(+6e^-\)

**selenase® has optimal bioavailability**
### Dosage recommendations

#### SIRS/Sepsis

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start of therapy 1. Day</strong></td>
<td>2000 µg selenium = 4 x selenase® 500 micrograms solution for injection (4 x 10 ml)</td>
<td>20 µg selenium/kg bw as selenase® 100/500 micrograms solution for injection</td>
</tr>
<tr>
<td><strong>From day 2 until clinical improvement</strong></td>
<td>1000 µg selenium = 2 x selenase® 500 micrograms solution for injection (2 x 10 ml)</td>
<td>10 µg selenium/kg bw as selenase® 100/500 micrograms solution for injection</td>
</tr>
</tbody>
</table>

**Multiple trauma, cranial trauma, burns, acute pancreatitis, acute myocardial infarction**

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<tr>
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<th>Children</th>
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</thead>
<tbody>
<tr>
<td><strong>Start of therapy Day 1-5</strong></td>
<td>1000 µg selenium = 2 x selenase® 500 micrograms solution for injection (2 x 10 ml)</td>
<td>10 µg selenium/kg bw as selenase® 100/500 micrograms solution for injection</td>
</tr>
<tr>
<td><strong>From day 6 until clinical improvement</strong></td>
<td>500 µg selenium = 1 x selenase® 500 micrograms solution for injection (1 x 10 ml)</td>
<td>5 µg selenium/kg bw as selenase® 100/500 micrograms solution for injection</td>
</tr>
</tbody>
</table>

**Total parenteral nutrition**

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous therapy</strong></td>
<td>200 µg selenium = 2 x selenase® 100 micrograms solution for injection</td>
<td>2 µg selenium/kg bw as selenase® 100 micrograms solution for injection</td>
</tr>
</tbody>
</table>

Recommendation for the administration of selenase®:
- separately from other infusions, if the pH is lower than 7
- at least 1 hour apart from administration of vitamin C

#### Reference values

<table>
<thead>
<tr>
<th></th>
<th>decreased</th>
<th>reference range</th>
<th>beginning toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>whole blood</strong></td>
<td>µg/l</td>
<td>µmol/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 100</td>
<td>100 - 140&lt;sup&gt;1&lt;/sup&gt;</td>
<td>≥ 1087&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>&lt; 1,3</td>
<td>1,3 - 1,8&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≥ 13,8&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>serum</strong></td>
<td>µg/l</td>
<td>µmol/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 80</td>
<td>80 - 120&lt;sup&gt;2&lt;/sup&gt;</td>
<td>≥ 900&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>&lt; 1,0</td>
<td>1,0 - 1,5&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≥ 11,4&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>summary of product characteristics biosyn  <sup>2</sup>Yang et al. 1989  <sup>3</sup>calculated from 12-20
selenase® is very well tolerated
modulates inflammatory and coagulation pathways
protects from endothelial and organ damage

Literature: