selenase®

a chance for your intensive care patients

very well tolerated

↓

modulates inflammatory and coagulation pathways

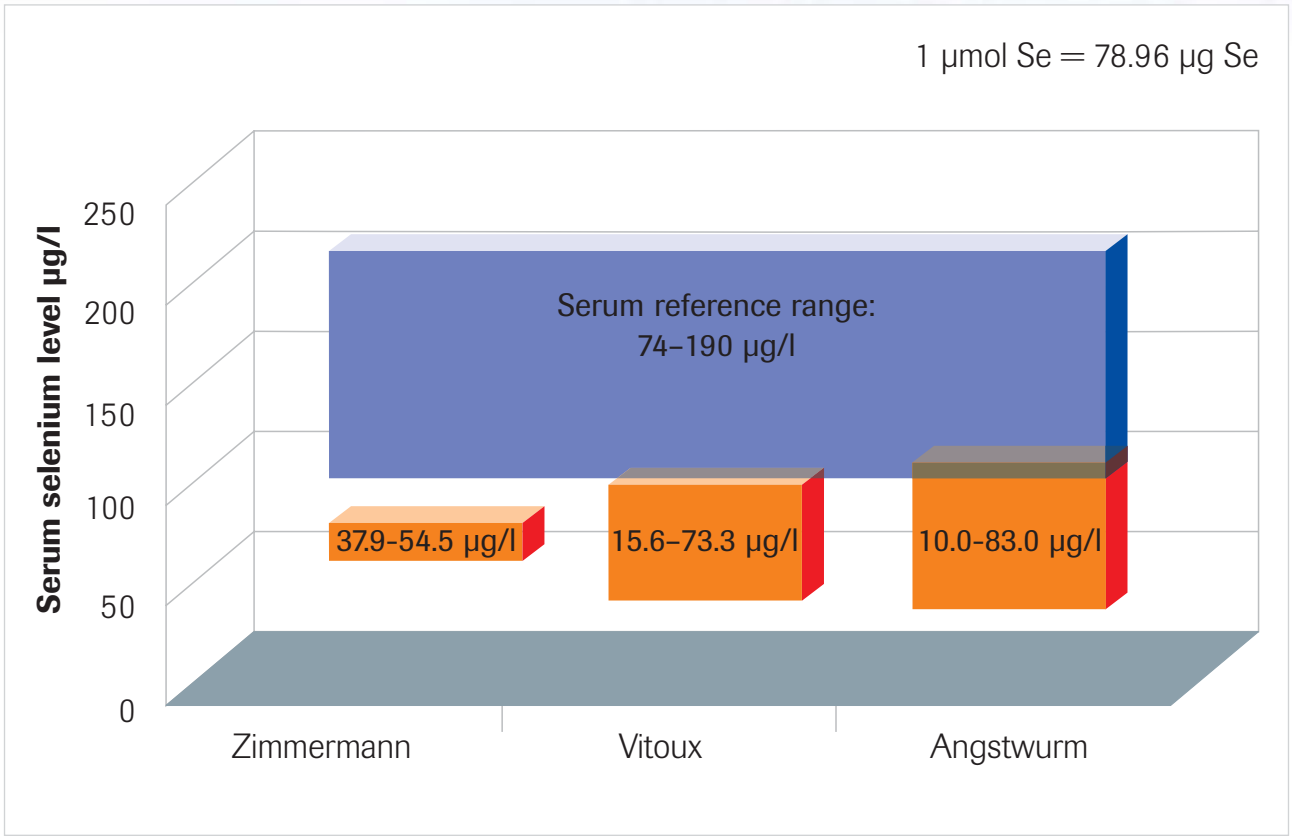
↓

protects from endothelial and organ damage

↓

reduces mortality

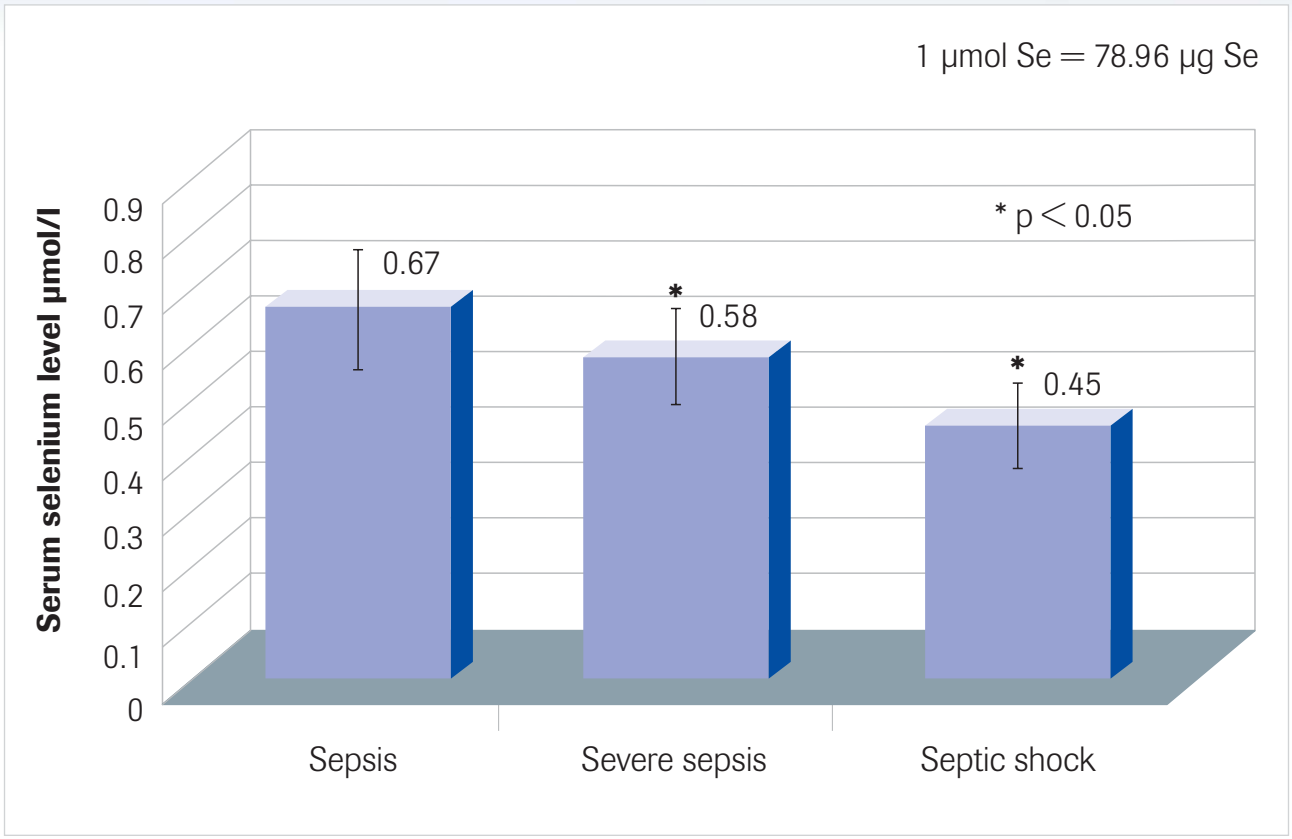
Initial serum selenium levels in sepsis compared to reference values



Sepsis patients have low selenium levels

Vitoux et al. 1996, Zimmermann et al. 1999, Angstwurm et al. 1999.

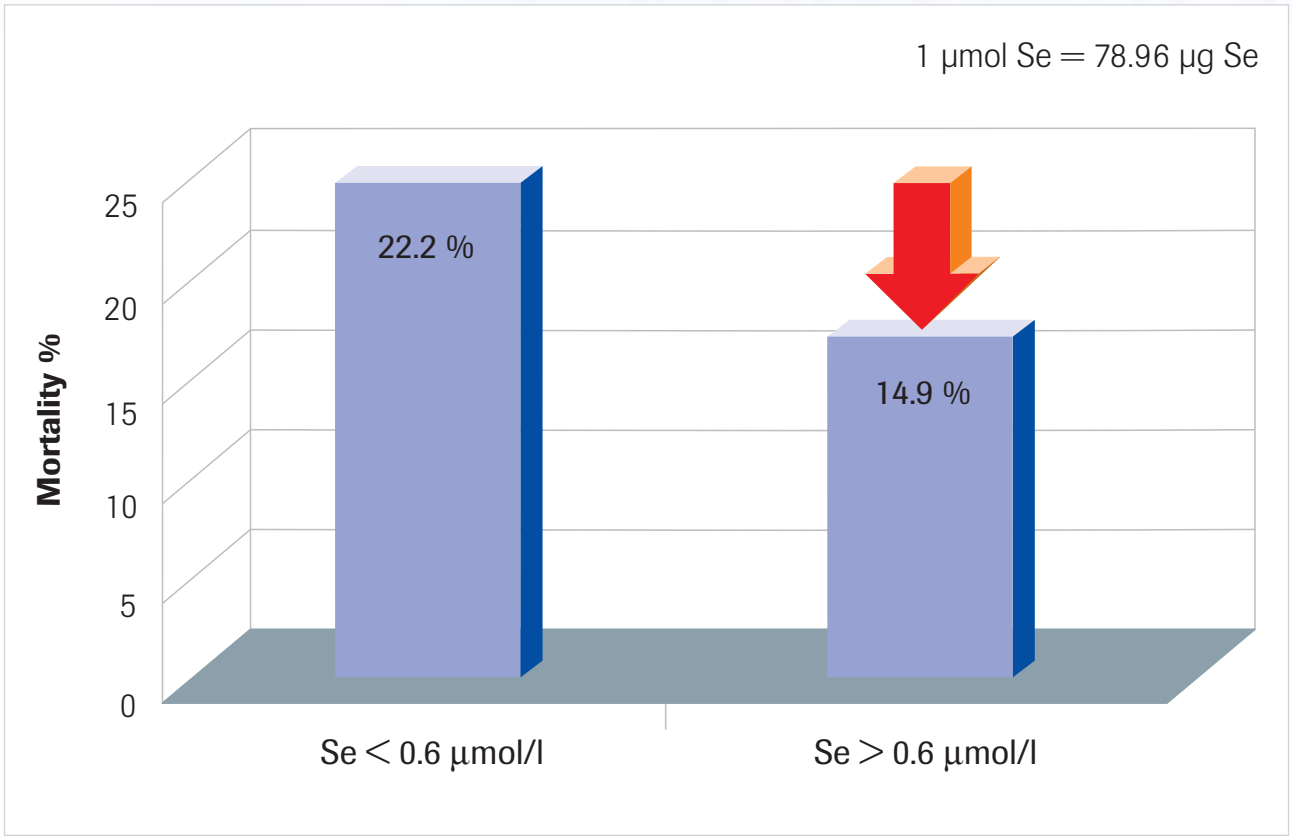
Initial serum selenium levels in relation to severity of sepsis



The more severe the sepsis, the lower the selenium level

Vitoux et al. 1996.

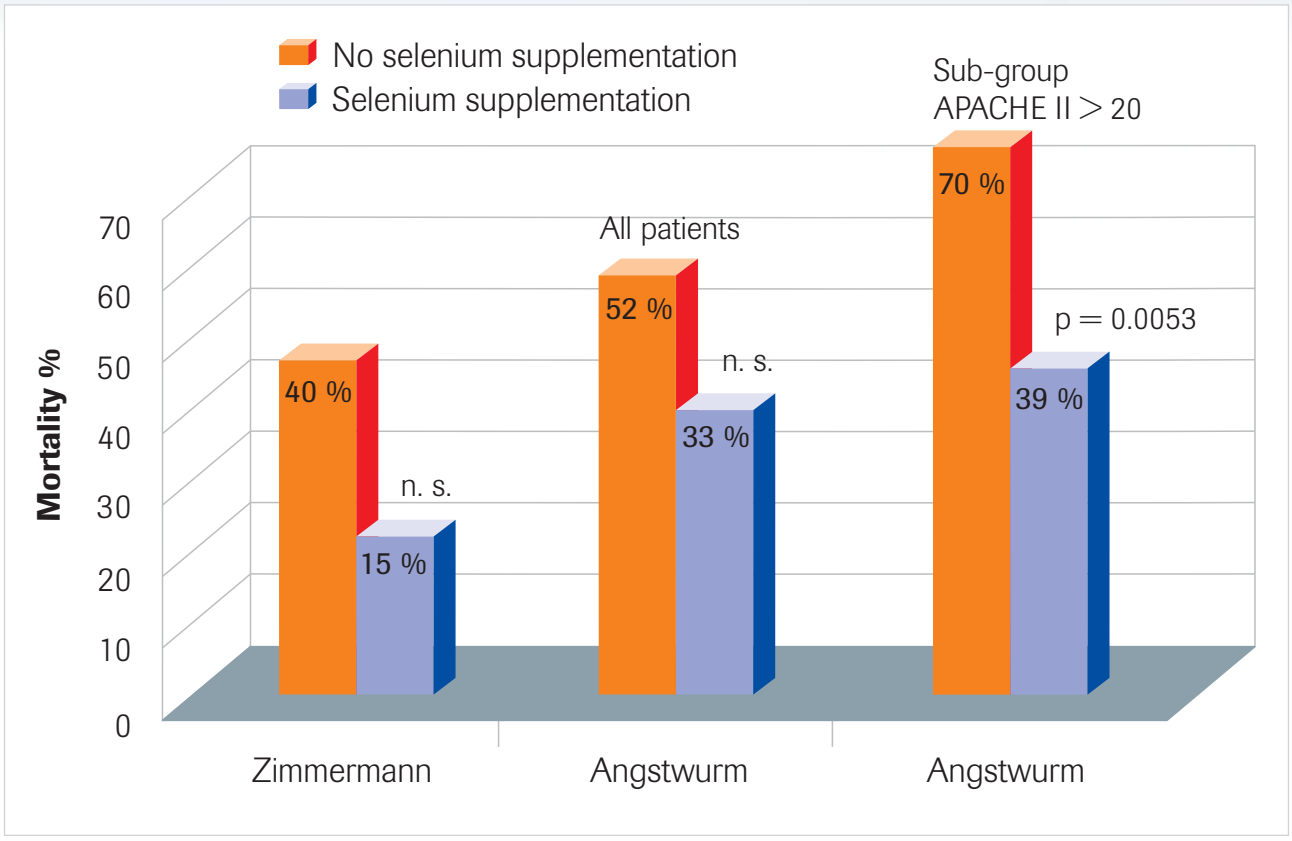
Mortality in relation to selenium level



The lower the selenium level, the higher the mortality

Vitoux et al. 1996.

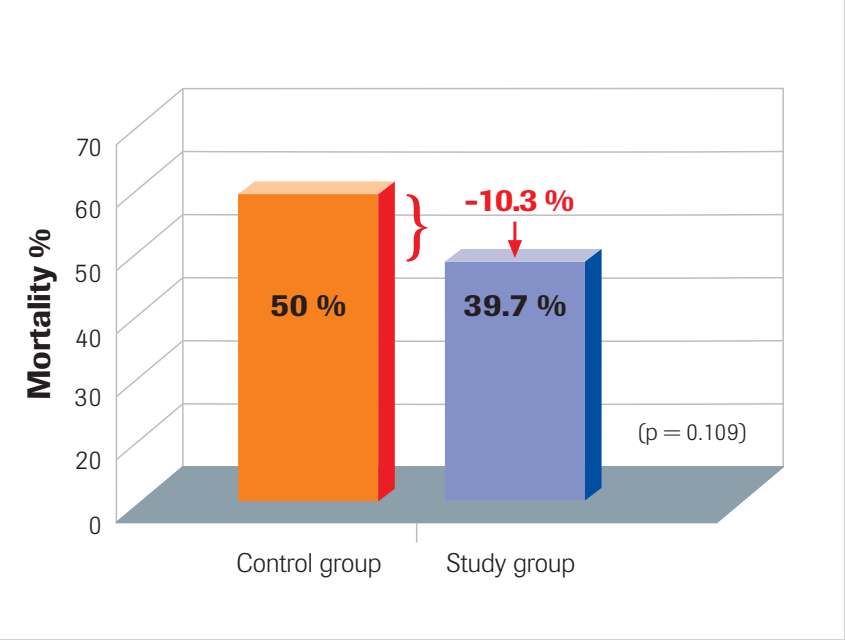
Change of mortality during selenase® supplementation



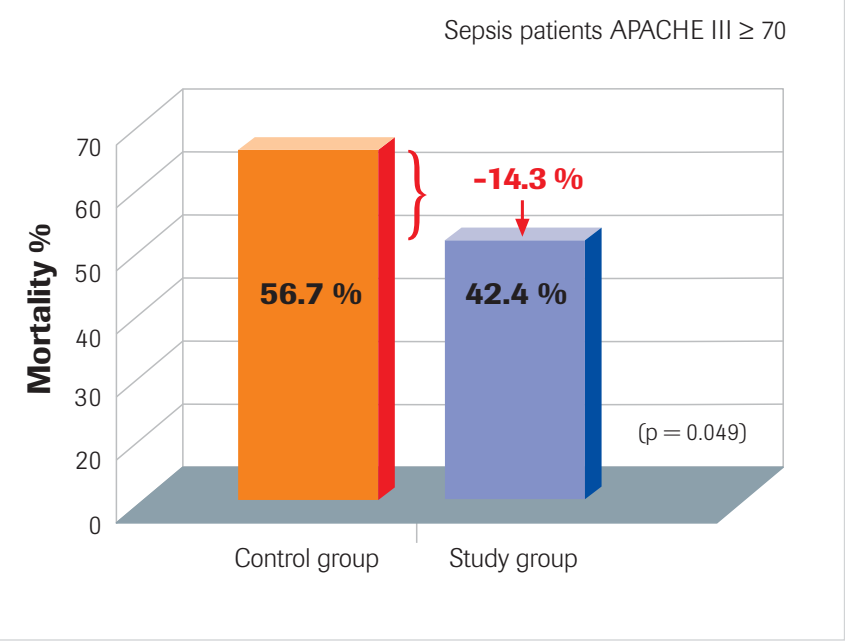
selenase® administration improves prognosis

SIC* study 2005: 28-day mortality

Intention-to-treat analysis,
data on file



Per-protocol group
data on file

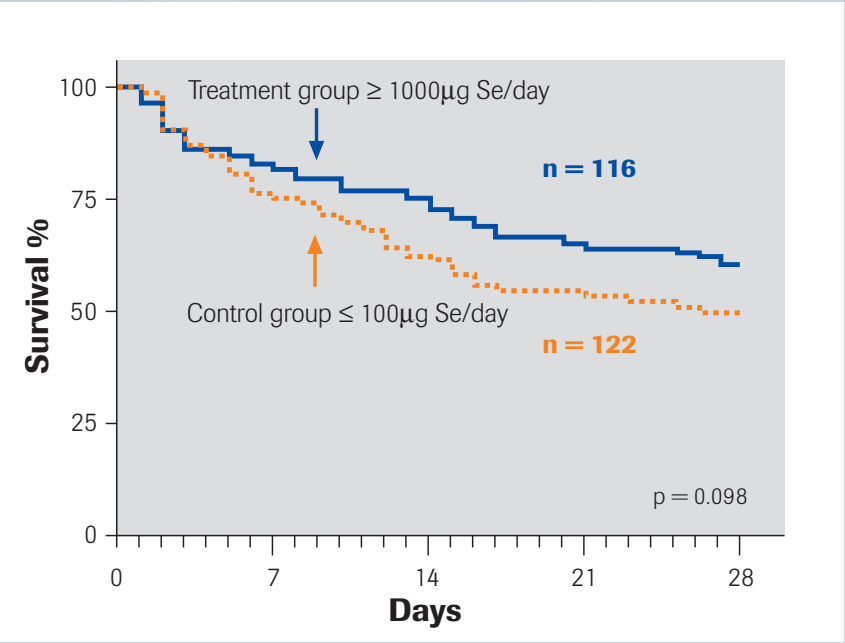


selenase® appreciably reduces mortality

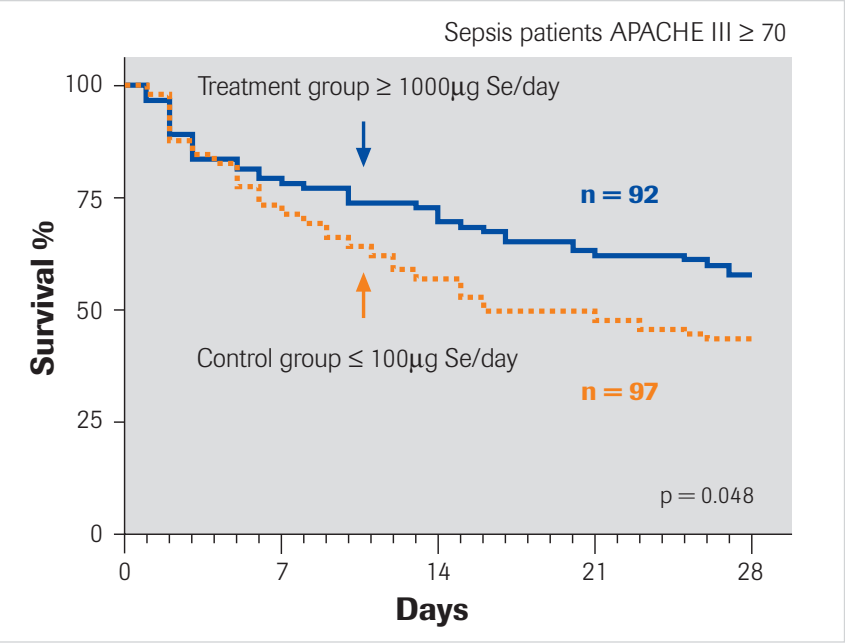
*selenase® in Intensive Care

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

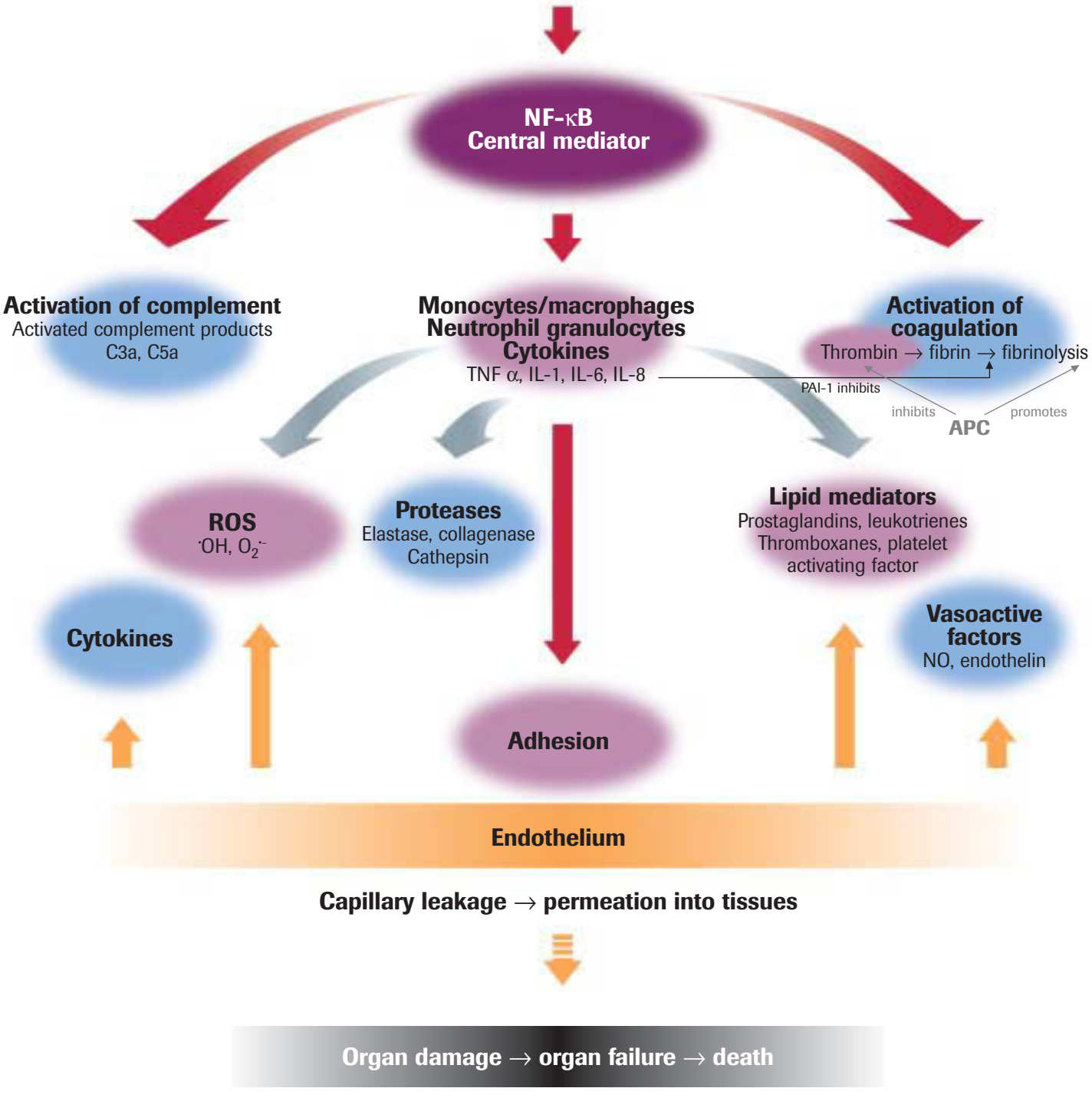


selenase® prolongs the duration of survival

*selenase® in Intensive Care

selenase® affects central metabolic

Pathophysiology of SIRS/Sepsis



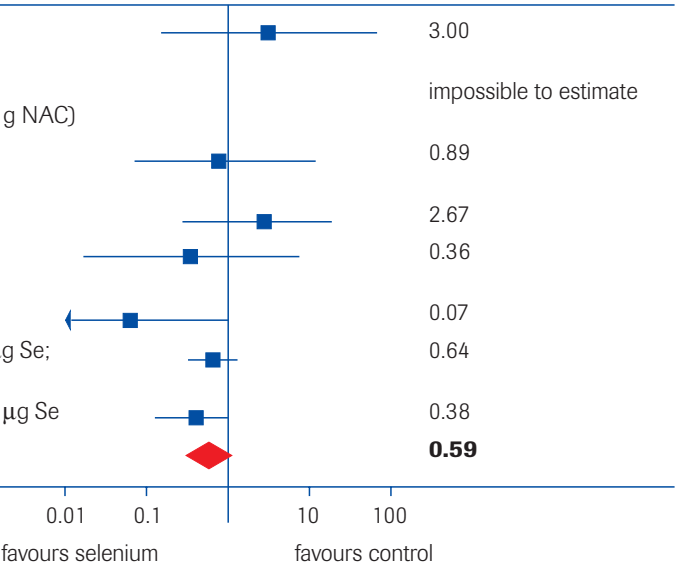
mediators

NF-κB	Selenite as well as increased GPX 1 and GPX 4 activity reduce NF-κB activation. (Brigelius-Flohé et al. 1997, 2003; Kretz-Remy et al. 1996)
Complement	Selenite reduces complement activation. (Hou 1997)
Cytokines	Selenium is essential for the immune system, acts as an immune modulator (antioxidant and anti-inflammatory). (Ferencik und Ebringer 2003; Rovensky et al. 2002)
ROS (Reactive Oxygen Species)	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)
Lipid mediators	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)
Adhesion	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)
Endothelium	**1.** Endothelial cells produce GPX 1, GPX 4 and TR. These regulate vascular tone (maintenance of $O2^{\bullet-}$/$NO^{\bullet}$-balance), cell adhesion (control of expression of cell adhesion molecules), apoptosis (inhibition/promotion of apoptosis-signal-regulating kinase 1), and eicosanoid production (control of activity of cyclooxygenases and lipoxygenases. **2.** An acidic milieu (inflammation) promotes the recruitment of SelP into the endothelium (protection against formation of peroxynitrite ($ONOO^-$) from superoxide anion ($O2^{\bullet-}$) and nitric oxide radicals ($NO^{\bullet}$). (Brigelius-Flohé et al. 2003)
Hydrocortisone	TR stabilize glucocorticoid receptors → better glucocorticoid response. (Grippo et al. 1985)
Insulin	Selenium stimulates the insulin signalling cascade, it has an insulin-like effect → improved control of glucose levels. (Hei et al. 1998, Pillay u. Makgoba 1992, Stapleton et al. 1997).

Glutathione peroxidases (GPX): GPX1: intra cellular, cytosolic, classical; GPX2: gastrointestinal; GPX3: plasma, extra cellular; GPX4: phospholipid-hydroperoxide, membrane bound. Selenoprotein P(SelP): extra cellular, endothelium bound. Thioredoxin-reductases (TR): TR1α/1, TR2β/2, TR3, intra cellular/extra cellular.

Why high-dose selenium?

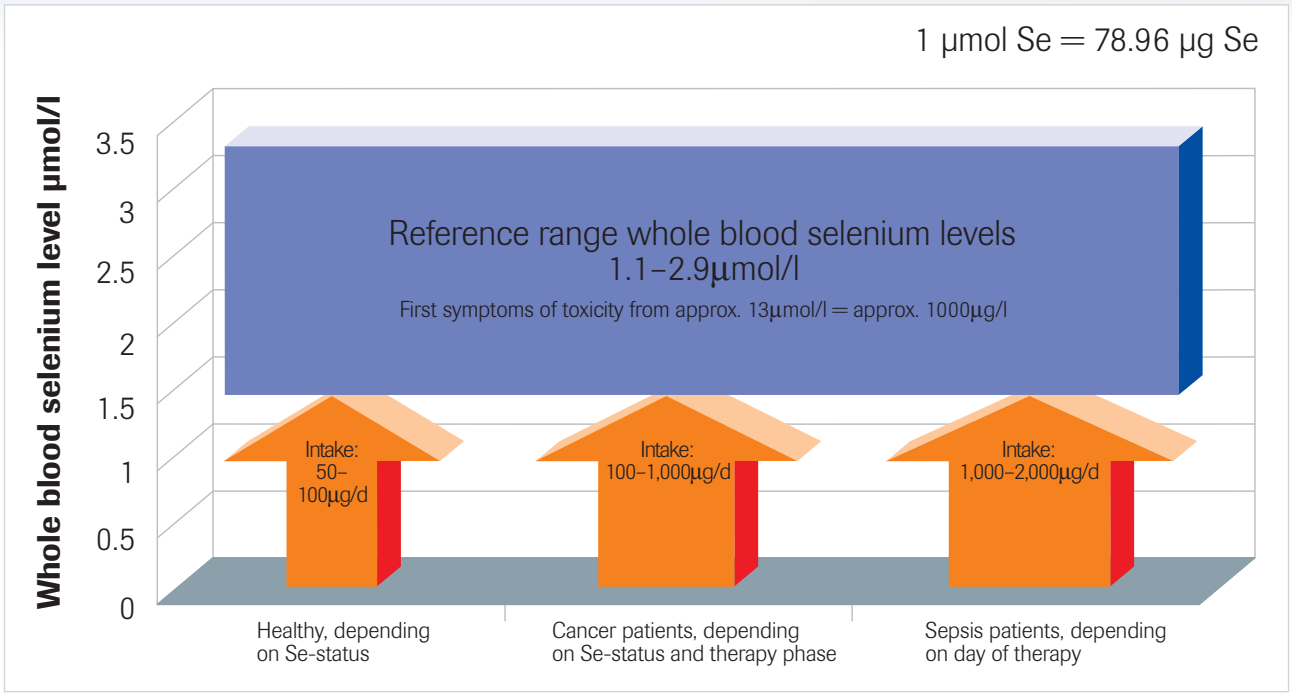
Author	Dose	relative risk (RR)
Berger 1998	Day 0-8: 159 µg Se (+ 40.4 µmol Cu + 406 µmol Zn)	3.00
Porter 1999	Day 0-7: 50 µg Se (+ 400 IE Vit E + 100 mg Vit. C + 8 g NAC)	impossible to estimate
Berger 2002	Day 1-14 or 21: 380 µg Se (+ 59 µmol Cu + 574 µmol Zn)	0.89
Berger 2001 a	Day 1-5: 500 µg Se/day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



Heyland et al. 2005[16]

Highest selenium dose – best outcome

Selenium safety



Literature at biosyn

Tolerability of selenium/selenase®

Selenium intake (healthy)

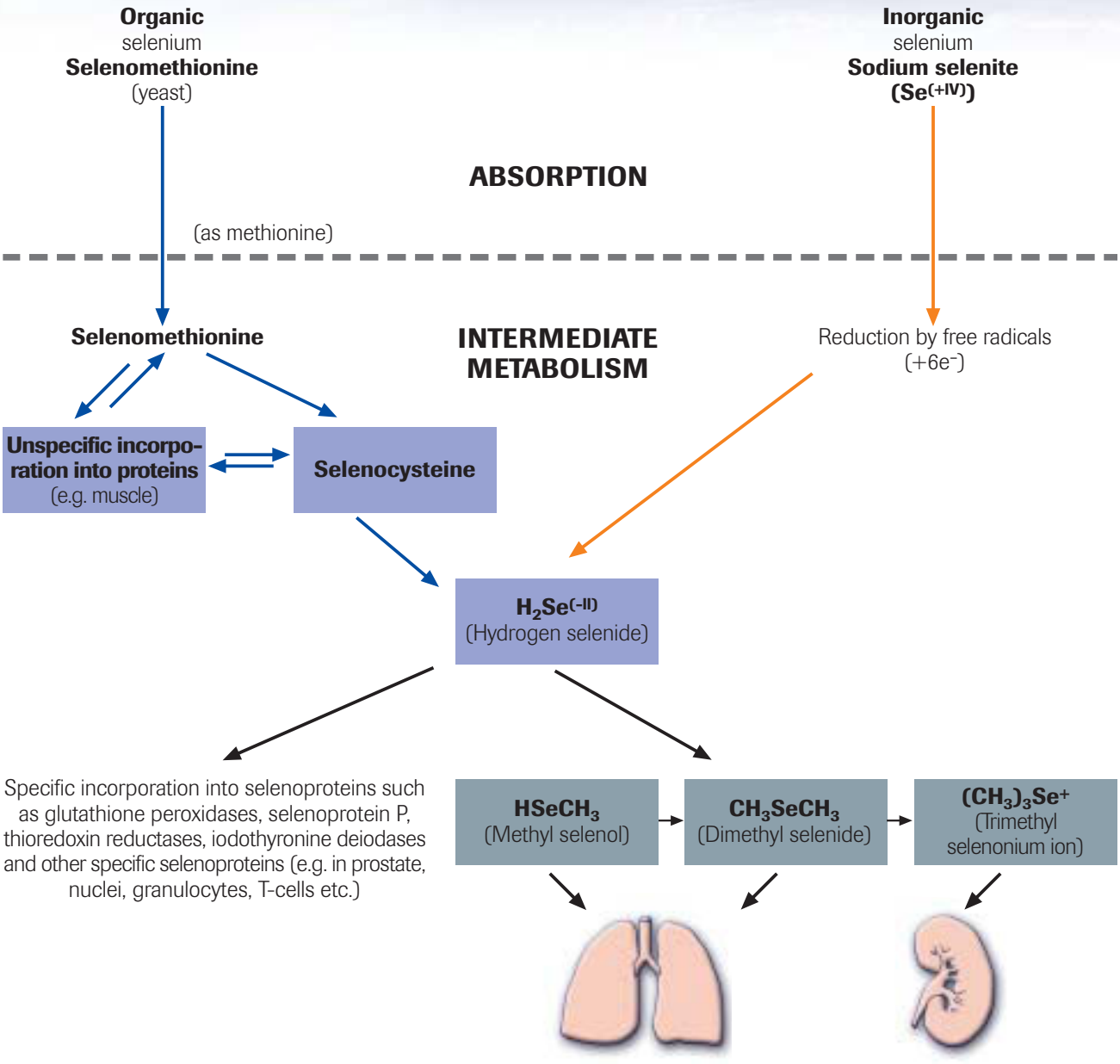
400–800 µg/day
= maximum chronic intake (years)

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)



selenase® has optimal bioavailability

Dosage recommendations

SIRS/Sepsis

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

Literature at biosyn

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

Daily dose	Adults	Children
Start of therapy Day 1-5	**1000 µg selenium =** 2 x selenase® 500 micrograms solution for injection (2 x 10 ml) 	**10 µg selenium/kg bw** as selenase® 100/500 micrograms solution for injection
From day 6 until clinical improvement	**500 µg selenium =** 1 x selenase® 500 micrograms solution for injection (1 x 10 ml) 	**5 µg selenium/kg bw** as selenase® 100/500 micrograms solution for injection

Literature at biosyn

Total parenteral nutrition

Daily dose	Adults	Children
Continuous therapy	**200 µg selenium =** 2 x selenase® 100 micrograms solution for injection 	**2 µg selenium/kg bw** as selenase® 100 micrograms solution for injection

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

Literature at biosyn

Reference values

		decreased	reference range	beginning toxicity
whole blood	µg/l µmol/l	< 100 < 1,3	100 - 140[1)] 1,3 - 1,8[3)]	≥ 1087[3)] ≥ 13,8[3)]
serum	µg/l µmol/l	< 80 < 1,0	80 - 120[1)] 1,0 - 1,5[3)]	≥ 900[2)] ≥ 11,4[3)]

[1)]summary of product characteristics biosyn [2)]Yang et al. 1989 [3)]calculated from [1)+2)]

selenase® corrects selenium deficiency

selenase®

- is very well tolerated
- modulates inflammatory and coagulation pathways
- protects from endothelial and organ damage

Literature: Angstwurm MWA, Schottdorf J, Schopohl J, Gaertner R: Selenium replacement in patients with severe systemic inflammatory response syndrome improves clinical outcome. Critical Care Medicine 27 (1999) 1807-1813. Brigelius-Flohé R, Banning A, Schnurr K. Selenium-dependent enzymes in endothelial cell function. Antioxid Redox Signal. 2003 Apr;5(2):205-15. Brigelius-Flohé R, Friedrichs B, Maurer S, Streicher R: Determinats of PHGPx espression in a cultured endothelial cell line. Biomedical and Environmental Sciences 10 (1997) 163-176. Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Lesher JL Jr, Park HK, Sanders BB Jr, Smith CL, Taylor JR: Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA 276 (1996) 1957-1963. Ferencik M, Ebringer L: Modulatory effects of selenium and zinc on the immune system. Folia Microbiol (Praha). 2003;48(3):417-26. Grippo JF, Holmgren A, Pratt WB: Proof that the endogenous, heat-stable glucocorticoid receptor-activating factor is thioredoxin. J Biol Chem. 1985 Jan 10;260(1):93-7. Hei YJ, Farahbakhshian S, Chen X, Battell ML, McNeill JH: Stimulation of MAP kinase and S6 kinase by vanadium and selenium in rat adipocytes. Mol Cell Biochem. 1998 Jan;178(1-2):367-75. Horvathova M, Jahnova E, Gazdik F: Effect of selenium supplementation in asthmatic subjects on the expression of endothelial cell adhesion molecules in culture. Biol Trace Elem Res. 1999 Jul;69(1):15-26. Hou JC: Inhibitory Effect of selenite and other antioxidants on complement-mediated tissue injury in patients with epidemic hemorrhagic fever. Biological Trace Element Research 56 (1997) 125-130. Kretz-Remy C, Arrigo AP. Selenium: a key element that controls NF-kappa B activation and I kappa B alpha half life. Biofactors. 2001;14(1-4):117-25. McKenzie RC, Arthur JR, Beckett GJ. Selenium and the regulation of cell signaling, growth, and survival: molecular and mechanistic aspects. Antioxid Redox Signal. 2002 Apr;4(2):339-51. Nève J: Methods in Determination of Selenium States. J. Trace Elem. Electrolytes Health Dis. 5 (1991) 1-17. Pillay TS, Makgoba MW: Enhancement of epidermal growth factor (EGF) and insulin-stimulated tyrosine phosphorylation of endogenous substrates by sodium selenate. FEBS Lett. 1992 Aug 10;308(1):38-42. Rovensky J, Svik K, Stancikova M, Istok R, Ebringer L, Ferencik M: Treatment of experimental adjuvant arthritis with the combination of methotrexate and lyophilized Enterococcus faecium enriched with organic selenium. Folia Microbiol (Praha) 2002; 47(5):573-8. Stapleton SR, Garlock GL, Foellmi-Adams L, Kletzien RF: Selenium: potent stimulator of tyrosyl phosphorylation and activator of MAP kinase. Biochim Biophys Acta. 1997 Mar 1;1355(3):259-69. Thomas L (Hrsg.): Labor und Diagnose. 6. Auflage. TH-Books Verlagsgesellschaft mbH, Frankfurt/Main 2000. Vitoux D, Forceville X, Gauzit R, Lahilaire P, Combes A, Chappuis P: Low plasma selenium in patients admitted in an intensive care unit is related to systemic inflammatory response syndrome and sepsis. Therapeutic Use of trace elements. Plenum Press, New York (1996) 127-131. Winnefeld K, Dawczynski H, Schirrmeister W, Adam G, Friedrich U, Hein S: Selenium in serum and whole blood in patients with surgical interventions. Biol Trace Elem Res 50 (1995) 149-155. Yang G, Yin S, Zhou R, Gu L, Yan B, Liu Y, Liu Y: Studies of safe maximal daily dietary Se-intake in a seleniferous area in China. Part II: Relation between Se-intake and the manifestation of clinical signs and certain biochemical alterations in blood and urine. J Trace Elem Electrolytes Health Dis 3 (1989) 123-130. Zhang F, Yu W, Hargrove JL, Greenspan P, Dean RG, Taylor EW, Hartle DK: Inhibition of TNF-alpha induced ICAM-1, VCAM-1 and E-selectin expression by selenium. Atherosclerosis. 2002 Apr;161(2):381-6. Zimmermann T, Albrecht S, Kühne H Vogelsang U, Grützmann R, Kopprasch S: Selensubstitution bei Sepsispatienten. Eine prospektiv randomisierte Studie. Med. Klin 92 (1997) (Suppl.III) 3-4.

Abbreviated Prescribing Information
selenase® 100 micrograms, solution for injection (50 micrograms/ml)
selenase® 500 micrograms, solution for injection (50 micrograms/ml)

Active ingredient: sodium selenite pentahydrate. **Composition:** Each 2 ml ampoule/10 ml injection vial contains 100 micrograms/500 micrograms selenium as 333 micrograms/1.66 mg sodium selenite pentahydrate ($Na_2SeO_3 \cdot 5H_2O$), corresponding to 50 micrograms/ml. **Excipients:** Sodium chloride, hydrochloric acid, Water for Injections. **Indication:** Proven selenium deficiency that cannot be offset from food sources. **Posology and Administration:** selenase®, solution for injection is administered as an intramuscular or intravenous injection at a daily dose of 100 – 200 µg (1.27 – 2.53 µmol) selenium. If necessary, this dose can be increased to 500 µg (6.33 µmol) for a typical adult. No dosage adjustment is required for paediatric, renal or hepatic impairment patients. **Contraindications:** Selenosis. **Interactions:** Ensure that the pH value does not fall below 7.0 and that the solution is not mixed with reducing substances (e.g. vitamin C). **Pregnancy and Lactation:** There are no data from the use of selenase® in pregnant or lactating women. **Undesirable Effects:** None known to date when used as directed. **Overdose:** Counter measures include gastric lavage, forced diuresis, dialysis or administration of high doses of vitamin C. **Pharmaceutical Precautions:** Store below 25ºC. **Legal Category:** POM. **Presentation:** Cartons containing 10 x 10 ml glass vials for single use. **MA Number:** PL 20437/0004. **MA Holder:** biosyn Arzneimittel GmbH, Schorndorfer Str 32, D-70734 Fellbach, Germany. **Date of Preparation:** November 2004.

We research.

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