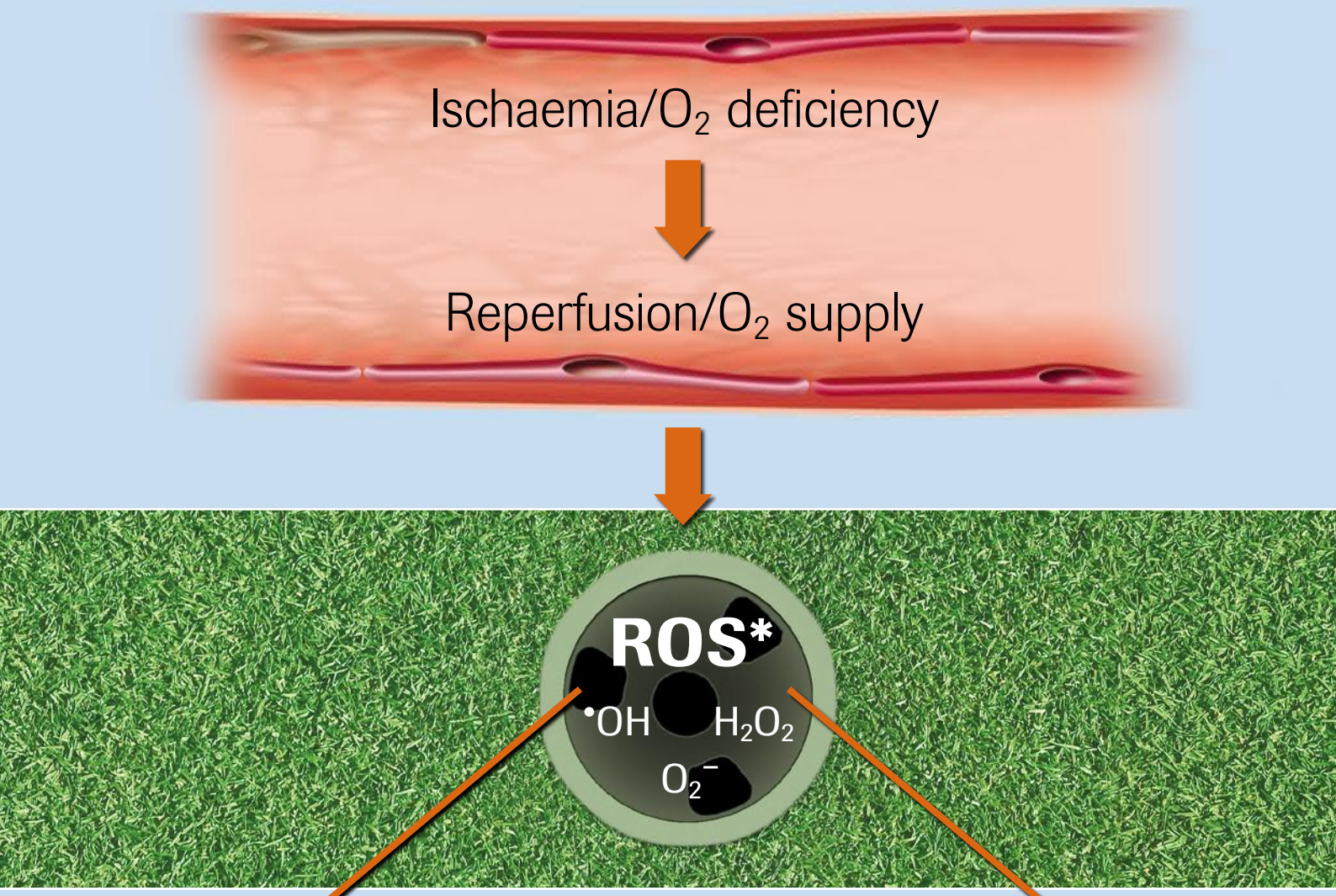
selenase®

a chance for your intensive care patients

Protection against reperfusion injury

- Sepsis
- Myocardial infarction
- Ischaemic stroke
- Transplantation
- Vascular surgery
- Plastic/reconstructive surgery
- Hypovolaemic shock, resuscitation

Tissue damage due to ischaemia/reperfusion



Reduced Antioxidant Capacity

Damage to Proteins, Lipids, DNA

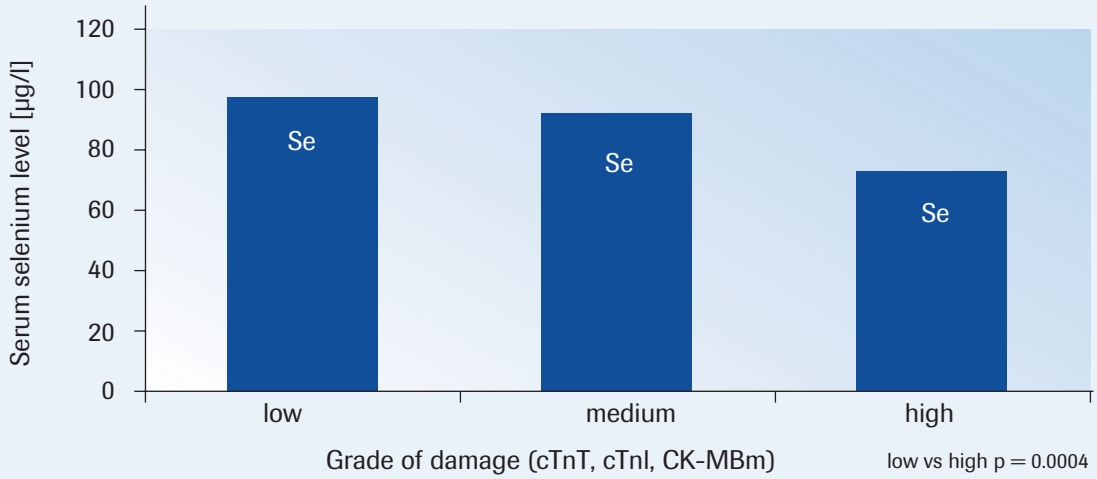
Cellular and Organ Damage

* Reactive Oxygen Species

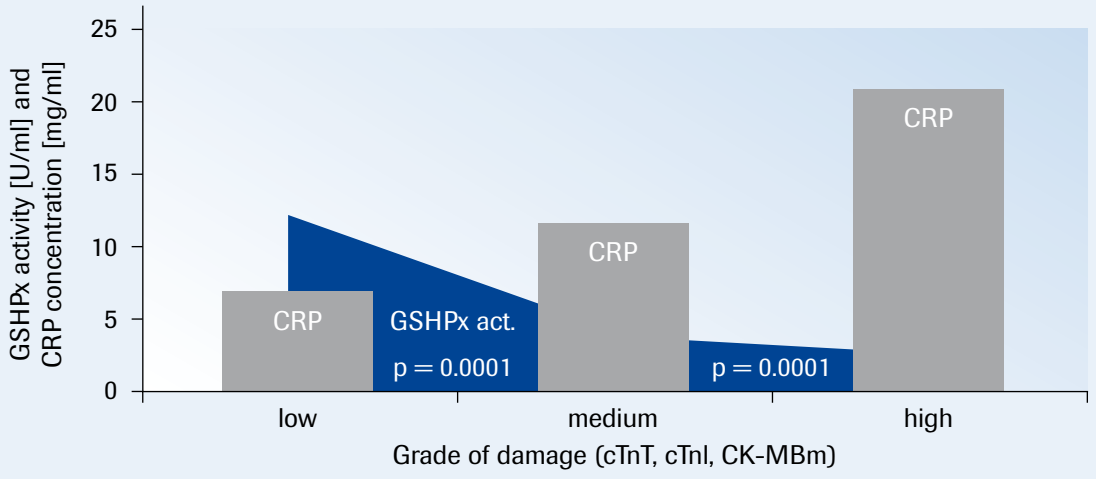
Selenium status correlates with the extent of damage

Altekin et al. 2005
Study in 70 patients with myocardial infarction

Correlation of selenium levels with the grade of cardiac damage



Correlation of CRP concentration and GSHPx activity with the grade of cardiac damage

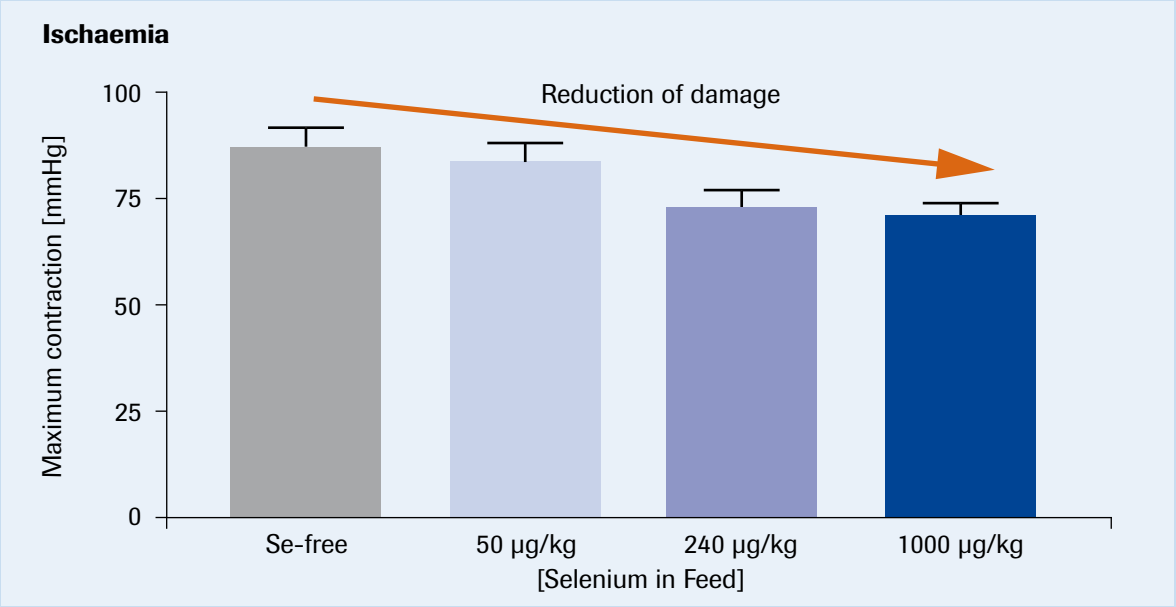


Grade of damage

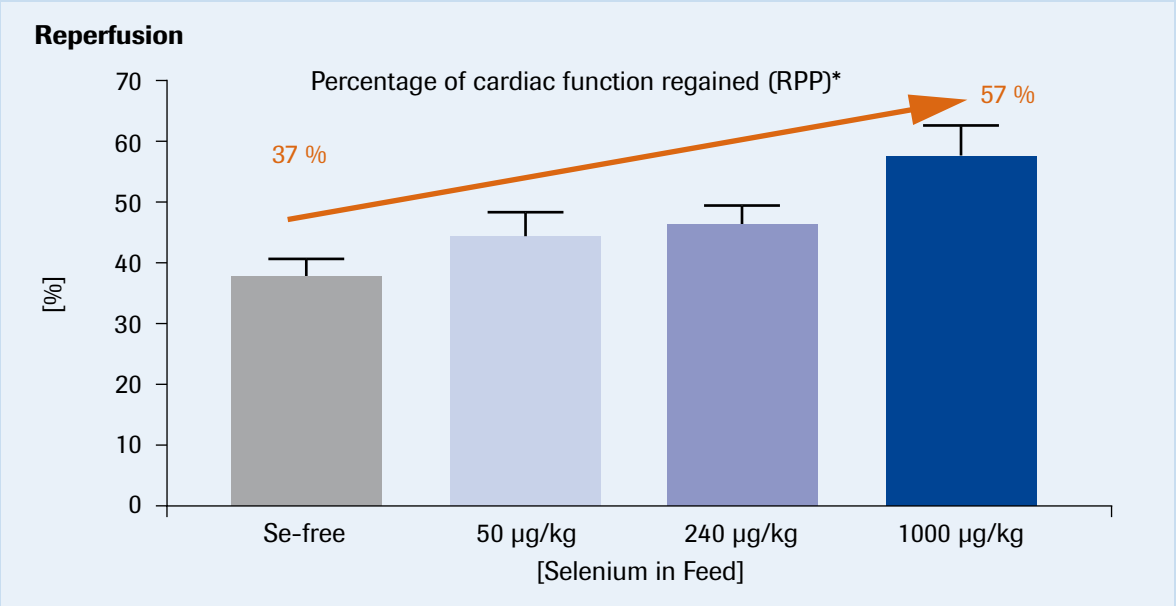
		cTnT [ng/ml]	cTnI [ng/ml]	CK-MBm [ng/ml]
low	(n=29)	0.1-0.3	0.2-0.5	7.0-10.0
medium	(n=14)	0.4-0.8	0.6-1.0	10.0-30.0
high	(n=27)	> 0.9	> 1.0	> 30

High selenite doses protect against ischaemia/reperfusion damage

Venardos et al. 2004:
Study in the isolated rat heart (pre-treatment for 5 weeks)



Ischaemic contraction at the end of the ischaemic phase is a measure for the severity of ischaemic damage.



Percentage of cardiac function regained after ischaemic and reperfusion phases.

*RPP (Rate Pressure Product) = Product of heart rate and blood pressure

selenase®

protects from ROS

- **Initially**
- **During ischaemia**
- **During reperfusion**

Successfully score!

- **reduce ROS**

Less damage to
- blood vessels
- tissues
- organs

Dosage recommendation*:

1000 µg selenium/day, until normal levels have been restored (cf. SIC Study (3): 2000 µg day 1; 1000 µg/day day 2 – 14)

*Further information on dosage and application see national SPC.

1 µmol Se = 78.96 µg Se

Action of selenite supplementation in ischaemia/reperfusion

For example:

Clinical chemistry

- Maintenance of antioxidant capacity (GSH/GSSG-ratio)
- Increase of expression and activity of ROS degrading selenoenzymes (glutathione peroxidases, thioredoxin reductases)
- Reduction of
  - Inflammatory markers (e.g. CRP)
  - Ischaemic markers in myocardial infarction (e.g. troponins, CK-MB)
  - Oxidative markers (e.g. malondialdehyde)
  - Redox signals (e.g. NF-κB activation)

Animal experiments

- Reduction of the extent of tissue damage
- Improvement of post-ischaemic mean arterial blood pressure (in myocardial I/R)
- Reduction of oedema (in cerebral I/R)

Effect of selenium on ischaemia/reperfusion injury

Selenium effect in general	Selenium effect in detail	Selenium level/dose
SEPSIS		
Selenium supplementation reduces mortality in sepsis patients (3, 15)	*Sepsis patients:* increase of glutathione peroxidase activity; reduction of MDA, NF-κB activity, IL-6, acute renal failure	Up to 1000 µg/day (2000 µg on day 1 only) up to 14 days i.v. as sodium selenite. *Med Klin 1997, Crit Care Med 2007*
MYOCARDIAL INFARCTION		
Selenium supplementation increases ischaemic tolerance in neonatal hearts (7)	*In hearts of immature rat foetuses:* increase of ischaemic tolerance, reduction of lipofuscin pigments and serum NO concentration	Oral pre-treatment of pregnant rats: 2000 µg/kg drinking water vs. 237 µg/kg feed *Chin Med J 2000*
Selenium levels correlate with the extent of myocardial damage (2)	*In 70 patients with myocardial infarction:* low selenium levels correlate with: inflammatory markers: CRP↑, prognosis markers: CK-MB↑, cardiac troponins↑	107 µg/l vs. 68 µg/l (median) (= 1.36 µmol/l vs. 0.86 µmol/l) *J Trace Elem Med Biol 2005*
Selenium supplementation increases antioxidant capacity and reduces cardiac damage (12)	*In isolated rat hearts:* dose dependent improvement of heart function, less reduction of GSH (vs. GSSG), reduction of increase in MDA as well as reduction of increased NF-κB values, reduced cardiac damage due to xanthine oxidase, $^{\bullet}OH$ or Ca^{2+}.	Selenium administration 10 min. before ischaemia and during 30 min. of reperfusion. Up to 78.7 µg/l selenium in perfusion medium. *Antioxid Redox Signal 2005*
Pre-ischaemic selenium status is the deciding factor for outcome (9)	*In Wistar rats:* high dose selenium diet: reduced extent of infarction, maintains postischaemic GSH/GSSG ratio; increases GPx activity; improves postischaemic average arterial blood pressure	1500 µg vs 50 µg Se/kg feed during 10 weeks *Antioxid Redox Signal 2004*
Sufficiently high doses of selenium increase tolerance of ischaemia and reperfusion (13)	*In isolated rat hearts:* increase of expression of thioredoxin reductases (Txrd-1, Txrd-2) and glutathione peroxidases (GPx-1, GPx-2), increase of I/R tolerance	Oral pre-treatment over 5 weeks: 1000 µg/kg vs. 240 µg/kg [sodium selenite/feed] *Mol Cell Biochem 2005*
Selenium supplementation before I/R increases the antioxidant capacity of the myocardium	*In 23/23 patients with acleistocardia or a defect of the interventricular septum:* no significant increase of Se blood levels but higher myocardial Se concentration and GPx-mRNA expression and activity, as well as lower MDA concentration	400 µg selenium over 7 days pre heart surgery *Zhonghua Y; Xul Za Zhi 1999* *Chin Med J 2000*
CEREBRAL STROKE		
Sufficiently high selenium doses protect against cerebral cell death due to Ischaemia/ Reperfusion (14)	*In Wistar rats:* positive effect on: ATP levels, intracellular Ca^{2+}, heat shock protein 70, caspase-3 activity; less oedema and cell separation with minimal microglial cell infiltration.	i.p. pre-treatment over 7 days: up to 100 µg/kg body weight as sodium selenite *Brain Res 2007*
Se-supplementation protects against neurodegeneration in cerebral ischaemia (4)	*In rats:* protection against neuronal lipidperoxidation	Pre-treatment over 7 days up to 200 µg/kg body weight as sodium selenite *Biol Trace Elem Res 2004*
VASCULAR SURGERY		
Selenite as a possible therapy to reduce peroxynitrite formation from NO in vascular surgery (1)	Theoretical observations on data of 40 patients with aortic aneurysm and peripheral arterial occlusive disease.	*Med Klin 1997*
ORGAN TRANSPLANTATION		
Selenite supplementation of the perfusion solution protects transplanted kidneys against oxidative damage (11)	*Animal model: Non-heart-beating donor:* malondialdehyde concentration in venous blood of donor kidneys is significantly reduced	Selenium supplementation over 120 minutes after organ donation *Transplant Proc 2003*

Literature on Reactive Oxygen Species in Intensive Care Medicine
A redox imbalance occurs during sepsis. Supplementation of antioxidant vitamins and enzymes can maintain the redox balance.
Bayir H: Reactive oxygen species. Crit Care Med 2005 Vol 33, No.12 (Suppl.)

selenase®

a chance for your intensive care patients

selenase® –

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

Literature

1. Albrecht S, Zimmermann T, Ockert D, Oelschläger S, Heinzmann J, Schilling JU. Verhindert Selen die Peroxinitritbildung aus NO bei gefäßchirurgischen Eingriffen? Med Klin (Munich). 1997 Sep 15;92 Suppl 3:10-1. **2. Altekin E,** Coker C, Sisman AR, Onvural B, Kuralay F, Kirimli O: The relationship between trace elements and cardiac markers in acute coronary syndromes. J Trace Elem Med Biol. 2005;18(3):235-42. **3. Angstwurm MWA,** Engelmann L, Zimmermann T, Lehmann C, Spes CH, Abel P, Strauß R, Meier-Hellmann A, Insel R, Radke J, Schüttler J, Gärtner R: Selenium in intensive care (SIC) study: Results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med 35 (2007) 1-9. **4. Ansari MA,** Ahmad AS, Ahmad M, Salim S, Yousuf S, Ishrat T, Islam F: Selenium protects cerebral ischemia in rat brain mitochondria. Biol Trace Elem Res. 2004 Oct;101(1):73-86. **5. Huang Y,** Bai H, Zhang Z: Mechanism of selenium protecting against free radical damages during myocardial ischemia/reperfusion in rats. Zhonghua Yi Xue Za Zhi. 1999b Nov;79(11):852-6. **6. Huang Y,** Liu Y, Zhang Z: Mechanism of selenium defending against free radical damages during myocardial ischemia/reperfusion in human. Zhonghua Yi Xue Za Zhi. 1999a Oct;79(10):731-4. **7. Liu D,** Liu S, Huang Y, Liu Y, Zhang Z, Han L: Effect of selenium on human myocardial glutathione peroxidase gene expression. Chin Med J (Engl). 2000 Sep;113(9):771-5. **8. Ostadalova I,** Vobecky M, Chvojkova Z, Mikova D, Hampl V, Wilhelm J, Ostadal B: Selenium protects the immature rat heart against ischemia/reperfusion injury. Mol Cell Biochem. 2007 Jun;300(1-2):259-67. Epub 2006 Dec 23. **9. Tanguy S,** Morel S, Berthonneche C, Toufektsian MC, de Lorgeril M, Ducros V, Tosaki A, de Leiris J, Boucher F: Preischemic selenium status as a major determinant of myocardial infarct size in vivo in rats. Antioxid Redox Signal. 2004 Aug;6(4):792-6. **10. Treska V,** Kuntscher V, Molácek J, Kobr J, Racek J, Trefil L: Can ischemia-reperfusion syndrome in transplanted kidneys procured from non-heart-beating donors be influenced by adding selenium into the reperfusion solution? An experimental study. Transplant Proc. 2003 Dec;35(8):3125-7. **11. Treska V,** Kuntscher V, Molácek J, Kobr J, Racek J, Trefil L: Can ischemia-reperfusion syndrome in transplanted kidneys procured from non-heart-beating donors be influenced by adding selenium into the reperfusion solution? An experimental study. Transplant Proc. 2003 Jun;35(4):1584-6. **12. Turan B,** Saini HK, Zhang M, Prajapati D, Elimban V, Dhalla NS: Selenium improves cardiac function by attenuating the activation of NF-kappaB due to ischemia-reperfusion injury. Antioxid Redox Signal. 2005 Sep-Oct;7(9-10):1388-97. **13. Venardos K,** Harrison G, Headrick J, Perkins A: Effects of dietary selenim on glutathione peroxidase and thioredoxin reductase activity and recovery from cardiac ischemia-reperfusion. J of Trace Elem in Med and Bio 18 (2004) 81-88. **14. Yousuf S,** Atif F, Ahmad M, Hoda MN, Khan MB, Ishrat T, Islam F: Selenium plays a modulatory role against cerebral ischemia-induced neuronal damage in rat hippocampus. Brain Res. 2007 May 25;1147:218-25. Epub 2007 Feb 17. **15. Zimmermann T,** Albrecht S, Kühne H Vogelsang U, Grützmann R, Kopprasch S: Selensubstitution bei Sepsispatienten. Eine prospektiv randomisierte Studie. Med. Klin 1997, 92 (Suppl.III) 3 - 4.

Abbreviated Prescribing Information

selenase® 500 micrograms, solution for injection (50micrograms/ml)

Active ingredient: sodium selenite pentahydrate. **Composition:** Each 10ml injection vial contains 500 micrograms selenium as 1.66mg sodium selenite pentahydrate ($Na_2SeO_3 \times 5H_2O$), 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 – 2.53µmol) 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 x10ml 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:** November2004

selenase® corrects selenium deficiency

Foreign distributors for selenase®

Great Britain	Oxford Nutrition Ltd.	info@nutrinox.com
Luxembourg	Promopharm S.A.	promopharm@pt.lu
Netherlands	Lamepro B.V.	lamepro@lamepro.nl
Austria	Richter Pharma	office@richter-pharma.at
Russia	Medicana Pharm	irinavitv@yahoo.de; irina_vitv@mtu-net.ru
Switzerland	Robapharm AG	info@robapharm.ch
Slovakia	Vivax Pharmaceuticals s.r.o.	bronislavciko@vivax.sk
South Korea	NMP Korea	smkang@kgbms.org
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We research.

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We would be pleased to send you any further information.

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