Selenium and stroke

selenase®

• eliminates selenium deficiency
• stroke impairs selenium status
• high selenium status correlates with positive outcome
Sodium selenite for stroke

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
<th>Se dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Bolus directly after admission to ICU</td>
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<tr>
<td>Day 2–5</td>
<td>Maintenance therapy</td>
<td>1,000 µg Se/day</td>
</tr>
</tbody>
</table>

*ongoing clinical trial

[A] NCT02505295 “Selenium and ischemic stroke outcome”.

By now a randomized, double-blinded, placebo controlled trial with the title “Selenium and ischemic stroke outcome” (NCT02505295) is under way, which investigates whether administration of 2,000 µg selenium in form of selenase® immediately after patient admission as well as 1,000 µg selenium per day (selenase®) for five days reduces mortality and neurological damage.

Sodium selenite for stroke

- Stroke patients show significantly reduced selenium levels[1]
- High glutathione peroxidase concentration correlates with low neurological deficiency and a positive outcome after a stroke[1]
- Significantly reduced selenoprotein P concentration in patients after an acute stroke[2]
- Reduced selenoprotein P status is associated with a significantly higher risk for stroke[2]
### Compatibility

<table>
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<tr>
<td>• 5% glucose solution</td>
<td>• Cytostatic agent solutions$^\text{[I]}$</td>
</tr>
<tr>
<td>• Ringer solution</td>
<td>• Amino acid solutions that contain cysteine$^\text{[II]}$</td>
</tr>
<tr>
<td>• Carbohydrate solutions</td>
<td>• Solutions that contain glutathione (GSH)$^\text{[III]}$</td>
</tr>
<tr>
<td>• Electrolyte solutions with increased potassium concentration</td>
<td>• Vitamin solutions that contain vitamin C$^\text{[IV]}$</td>
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<tr>
<td>• Crystalloid electrolyte solutions</td>
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$^\text{[I]}$ Selenase® should generally be administered considerably before the cytostatic agent.

$^\text{[II, III]}$ SH groups react with sodium selenite; sodium selenite can no longer fulfill its task as a radical scavenger.$^\text{[A]}

$^\text{[IV]}$ Selenium ($\text{Se}^{\text{IV}}$) in sodium selenite is reduced by vitamin C to the elementary selenium ($\text{Se}^0$) and is thereby ineffective.$^\text{[B–D]}

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## Summary

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<tr>
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<td>• the preservation of the mitochondrial respiratory chain</td>
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Selenium plays an important role in the brain.
Selenium in the brain

At a glance

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Selenium is essential for the brain

The total amount of selenium in the brain is comparatively low. In the brain, a concentration of $110 \pm 21$ ng selenium/g wet weight was determined in German adults. In contrast, there is $771 \pm 169$ ng selenium/g in the kidney and $291 \pm 78$ ng selenium/g in the liver. The brain thus contains only 2.3% of the entire selenium in a human body.\[^{[3]}\] Preferentially the available selenium is transported to the brain at the expense of other organs, such as the liver, if mammals are on a long-term low selenium diet.\[^{[4]}\] Approximately 20% of the entire selenium amount in the brain is incorporated into glutathione peroxidase.\[^{[4]}\] With a sufficient selenium supply, the glutathione peroxidase activity in the liver is 13 times greater than in the brain (animal experiment). After a selenium-deficit diet of about 6 months, the activity of the glutathione peroxidase was reduced by 92% in the liver, while in the brain it only declined negligibly.\[^{[8]}\]

Selenium plays an important role for various diseases of the central nervous system (CNS), among others stroke, brain tumors, brain development and neurodegenerative diseases.\[^{[6]}\] First indications were delivered by reports about neurological diseases in patients with low selenium status or restricted selenoprotein biosynthesis. Over a long time period, parenterally nourished patients with inadequate selenium content developed among others progressive encephalopathy.\[^{[7]}\] Two rare mutations of the human SEPSECS gene that codes the selenocysteine synthase lead to progressive cerebellar and cerebral atrophy.\[^{[8]}\]
Glutathione peroxidase 1 influences the infarct volume

As already long known, mice with knock-out of glutathione peroxidase 1 (GxP1) show a 3-fold increase of infarct volume compared with wild-type mice (p<0.01) (Fig. 1). This is also reflected in the increased number of necrotic and apoptotic cells. An earlier activation of caspase 3 in GPx1 knock-out mice moreover indicates increased susceptibility to apoptosis in GPx1 knock-out mice.

Furthermore, an investigation with transgenic mice, which overexpressed glutathione peroxidase, revealed a significant reduction in the infarct volume in consequence of I/R damage compared with non-transgenic mice. An overexpression of glutathione peroxidase significantly reduced both necrotic as well as apoptotic cell death in endangered brain regions (p<0.05). In these animals, the activation of astrocytoma and microglia in the ischemic brain was reduced. In contrast to wild type-mice, glutathione peroxidase overexpressing mice showed a significantly better preserved tissue structure and a reduced infiltration of acute inflammatory cells (p<0.05).
3-fold increased infarct volume for glutathione peroxidase 1 (GPx1) knock-out mice

![Infarct Volume Graph]


*Fig. 1*
Glutathione peroxidase 4: essential for brain development

Glutathione peroxidase 4 (GPx4) is essential for survival. Homozygous GPx4 knock-out mice die in utero in the middle trimester due to malformations. GPx4 is expressed in neurons, particularly in the hippocampus. Meanwhile, it was demonstrated that the neuronal GPx4 expression plays an essential neuroprotective role in Morbus Parkinson. In addition, GPx4 modulates the interneuronal development in the nerves of the nigrostriatic pathway as well as the expression of parvalbumin. Furthermore, GPx4 prevents seizures and neurodegeneration.

Glutathione peroxidase-4 plays a role in neuropathological diseases

GPx4 is a multifunctional antioxidative protein with anti-apoptotic characteristics. This is particularly relevant because neurons, in contrast to glial cells, essentially depend on their GPx activity to detoxify free oxygen radicals (ROS) and lipid peroxides. Increased ROS levels occur in neuropathological disorders such as trauma, seizure and ischemia. Furthermore, it has been shown that the cytosolic variants of GPx4 are up-regulated after brain injuries. However this does not occur in neurons, but rather in reactive astrocytes, a glial cell type that does not express GPX4 under normal conditions. After brain injuries, astrocytes change their cytoskeleton and migrate in the direction of the lesion, where they are involved in the repair of oligodendrocytes and myelination, as well as in the re-establishment of the blood-brain barrier in order to prevent neuroinflammation. Therefore expression of GPx4 in the astrocytes is therefore a response to stress that provides neuro-protection to prevent additional damage. A sodium selenite administration in the physiological range with zebra fish significantly increased the GPx4 expression in the brain compared to selenium-deficient zebra fish (p = 0.048) (Fig. 2). Apart from GPx4, other selenoproteins such as SEPN1 and GPx3 also have neuroprotective functions by neutralizing reactive oxygen species.

Overall, these results suggest that a sodium selenite administration increases the antioxidative capacity of the brain.
Sodium selenite administration in the physiological range significantly increases GPx4 expression in the brain


*Fig. 2*
Selenoprotein P knock-out causes severe neurological dysfunction

Almost all known selenoproteins can be found in the brain, whereby the transport protein for selenium, selenoprotein P (SEPP1), makes selenium available in the form of selenocysteine for the expression of selenoproteins. An animal study showed that selenium from SEPP1 could be detected in the brain even after two hours. This indicates that the brain has an uptake mechanism for SEPP1.\textsuperscript{[18]} The “knock-out” of SEPP1 leads to decreased selenium concentration and selenoprotein activities in the brain.\textsuperscript{[19,20]} SEPP1 knock-out mice developed brain function disorders and showed limited motor coordination with an adequate selenium diet provided by sodium selenite.\textsuperscript{[21]} However, the neurological disorders with an adequate selenium diet using selenomethionine were so massive that almost half of the SEPP1 knock-out mice had to be euthanized. A sodium selenite administration above the daily normal selenium requirement could prevent brain function disorders (\textit{Fig. 3}).\textsuperscript{[21]}

Moreover, significantly greater neurological dysfunctions occurred with male animals in SEPP1 knock-out mice (p<0.001).\textsuperscript{[22]} Treatment with sodium selenite attenuated the motoric deficits of male animals to a greater degree (p<0.001).
SEPP1 knock-out mice: improvement of brain function disorders with supraphysiological administration of sodium selenite


Fig. 3
Sodium selenite for stroke

At a glance

Animal and cell studies show:

Sodium selenite acts neuroprotectively even hours after induction of the damage

Selenium deficit results in massively increased susceptibility to excitotoxicity and greater neuronal cell loss

According to studies, the neuroprotective effect of sodium selenite is based on:

• the reduction of oxidative stress in neurons
• the preservation of the mitochondrial respiratory chain
• the inhibition of NFκB- and AP1 activation
• the inhibition of the ischemia-induced DNA oxidation
• the normalization of ischemia-activated autophagy

Sodium selenite acts neuroprotectively even hours after induction of the damage

Savaskan et al. investigated the role of selenium for stroke in vitro and in animal experiments. Glutamate was employed for the simulation of a stroke. It is the predominant stimulating neurotransmitter in the brain. Under pathological conditions such as stroke, epilepsy and traumatic brain damage, glutamate can be toxic for neurons. Experiments have shown that simultaneous administration of sodium selenite in a concentration-dependent manner prevented glutamate-induced cell death (p < 0.01) (Fig. 4), whereby the greatest effect (98% protection) was determined for a concentration of 100 nM sodium selenite, a concentration that lies in the human physiological range. Glutamate-induced cell death could not only be prevented with the simultaneous administration of sodium selenite, but reduced also with a sodium selenite administration two hours after the glutamate-induced damage (p < 0.001) (Fig. 5). These results were confirmed in an additional study by Mehta et al. Both a significant neuroprotective effect of sodium selenite with glutamate toxicity as well as with hypoxia (p < 0.001 or p < 0.05) was demonstrated.
Concentration-dependent neuronal protection of sodium selenite

![Graph showing concentration-dependent neuronal protection of sodium selenite.](image)


*Selenium deficiency increases susceptibility to glutamate-induced excitotoxicity.*

**Fig. 4**

A sodium selenite administration in the physiological range after 2 hours reduced neuronal death

![Graph showing A sodium selenite administration in the physiological range after 2 hours reduced neuronal death.](image)


*Selenium deficiency increases susceptibility to glutamate-induced excitotoxicity.*

**Fig. 5**
The comparison of neurological damage in ischemia with and without sodium selenite administration revealed significantly less neurological deficits with an intervention of sodium selenite (p < 0.05 or p < 0.01) (animal experiment) (Fig. 6). Also the death of brain cells with ischemia was significantly reduced by 38% with sodium selenite administration (p<0.05) (Fig. 7).

A 7-day sodium selenite treatment before ischemia resulted in a significant reduction of brain damage in vivo (p<0.01) (Fig. 8). The infarct volume was thereby reduced from 36.4±24.5% to 11.6±5.0% compared to the control group 24 hours after re-establishment of the circulation. This in vivo result clearly shows the neuroprotective effect of sodium selenite for strokes.

**Significant improvement of the neurological outcome in sodium selenite group**

[Graph showing behavioral scores for flexion and spontaneous movement with control, ischemia, ischemia + sodium selenite, and sodium selenite conditions, with p-values indicated for each comparison.]

*Modified according to: Yousuf S et al. Brain Res. 2007 May 25; 1147: 218-25. Selenium plays a modulatory role against cerebral ischemia-induced neuronal damage in rat hippocampus.*
Significantly lower induction of apoptosis in the sodium selenite group

Modified according to: Yousuf S et al. Brain Res. 2007 May 25; 1147: 218-25. Selenium plays a modulatory role against cerebral ischemia-induced neuronal damage in rat hippocampus.

Fig. 7

Sodium selenite reduces brain damage caused by ischemia


Fig. 8
Selenium deficit massively increases susceptibility to excitotoxicity and increased neuronal cell loss

In order to confirm this in vitro result, rats were administered a selenium-adequate or deficient diet. The result confirmed the hierarchy of selenium distribution under selenium-deficit conditions. A selenium-poor diet in rats resulted in a dramatic reduction of the selenium concentration in the liver (p < 0.001), while in the brain, the selenium level was significantly reduced but only by 10% (p < 0.01) (Fig. 9).

In a kainate model (kainate = structural analogs of glutamate) for excitotoxicity it was however shown that this 10% reduction of the selenium level in the brain sufficed to produce significantly higher seizure rates (p < 0.01) (Fig. 10). Moreover, selenium-deficit rats showed significantly more apoptotic neurons and the neuronal cell loss in the hippocampus was significantly higher than in rats fed a selenium-adequate diet (p < 0.01) (Fig. 11).

Preferential selenium supply of the brain in case of selenium deficiency

Modified according to: Savaskan NE et al. FASEB J. 2003 Jan; 17(1): 112-4. **Selenium deficiency increases susceptibility to glutamate-induced excitotoxicity.**
Selenium deficit leads to significantly higher seizure rates in the brain

![Seizure activity graph](image)


Fig. 10

Higher neuronal cell loss in the hippocampus with low selenium diet

![Neuronal cell loss graph](image)


Fig. 11
Principle of action of neuronal protection by sodium selenite

Sodium selenite reduces oxidative stress in neurons

A surplus of glutamate induces high levels of reactive oxygen species (ROS) in neurons and thereby strongly increases oxidative stress. Sodium selenite administration prevents the production of ROS (p < 0.01) (Fig. 12), while having no influence on the glutathione level.[23] Also in the study by Mehta et al, sodium selenite significantly reduced the production of ROS induced by glutamate toxicity and hypoxia (p < 0.001 or p < 0.05).[24] This leads to the conclusion that the underlying mechanisms of sodium selenite-mediated neuronal protection lie in the significant attenuation of oxidative stress.

Sodium selenite reduces the incidence of oxidative stress in stroke patients

Sodium selenite preserves the mitochondrial respiratory chain after hypoxia

Hypoxia significantly reduces the activity of the complex I–IV of the respiratory chain (p<0.01). Cell studies have shown that pretreatment with sodium selenite first increases the activity of the individual complexes to the baseline value, and secondly significantly reduces the inhibiting effect of the hypoxia on the respiratory chain (Table 1). An administration of sodium selenite thus alleviated the negative effect of hypoxia on the mitochondrial respiratory chain, whereby the activity of the complexes either remained at a normal level or significantly improved compared to the condition without sodium selenite.

Sodium selenite inhibits NFκB- and AP-1 activation

Glutamate treatment resulted in increased nuclear NFκB and AP-1 level. This increase could be inhibited by sodium selenite. The gel-shift assay showed clearly that the glutamate-induced activation and bonding of NFκB and AP-1 on their “nuclear response elements” was reduced by sodium selenite. The missing activation of NFκB and AP-1 prevents neuronal cell death and reduces the activation of glial cells. The glial activation raises stress signals and neuronal damage to a higher power, which leads to secondary cell death (”second hit”).

<table>
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<tr>
<th>Complex</th>
<th>Hypoxia</th>
<th>Hypoxia + sodium selenite</th>
<th>p value</th>
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<tr>
<td>Complex I</td>
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<tr>
<td>Complex II + III</td>
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<tr>
<td>Complex IV</td>
<td>-24 %</td>
<td>-3 %</td>
<td>p&lt;0.001</td>
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Effect of sodium selenite is dependent on the biosynthesis of selenoproteins

In contrast to sodium selenite, sodium selenate has no direct antioxidative characteristics, but rather is only incorporated in selenoproteins. After sodium selenite was replaced by sodium selenate, most of the neuroprotective protection (70%) remained preserved. \(^{[23]}\) This suggests that the neuroprotective effect of sodium selenite depends on the biosynthesis of selenoprotein. The addition of cycloheximide, which inhibits protein biosynthesis, cancelled the neuroprotective effect of sodium selenite thereby supports the hypothesis (Fig. 13).

Sodium selenite reduced ischemia-induced DNA oxidation

Mehta et al. conducted an animal experiment to examine as well if cerebral ischemia induces oxidative DNA damage. \(^{[24]}\) The evidence of 8-OHdG revealed a significant increase in the oxidative damage 24 hours after re-establishment of circulation. In comparison to this, a pretreatment with sodium selenite significantly reduced the oxidative DNA damage (p<0.05) (Fig. 14). This shows that the antioxidative effect of sodium selenite consists of avoiding DNA oxidation and the damages it causes.
The addition of the protein synthesis inhibitor cycloheximide cancels the neuroprotective effect of sodium selenite.


Fig. 13

Sodium selenite reduces DNA oxidation induced by ischemia.


Fig. 14
Sodium selenite normalizes ischemia-activated autophagy

In order to remove damaged organelles and cell debris after a cerebral ischemia, autophagy is activated. LC3-II is a marker of autophagy. The measurement of LC3-II after an induced ischemia revealed in animal studies a significant increase after five hours (p < 0.001) and a decline to the original level after 24 hours (Fig. 15).[24] In rats that received sodium selenite for seven days, the increase of LC3-II after five hours was significantly lower (p < 0.001). After 24 hours the LC3-II level reduction was highly significant compared to the control group (p < 0.001). A pretreatment with sodium selenite prevented brain damage caused by ischemia, which is why there was less activation of autophagy.[24]

Sodium selenite inhibits the activation of autophagy after cerebral ischemia

![Graph showing LC3-II relative intensity over time with significance levels](image)


Fig. 15
Impact of a selenium deficit on the brain affected by stroke

See figure 16.

Effect of a selenium deficit (right side) on the brain affected by stroke, ischemia and brain trauma*

* Results from animal experiments and in vitro studies


Fig. 16
Selenium status and selenoprotein activity in the event of a stroke

At a glance

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<td>A reduced selenoprotein P status is significantly associated with a higher stroke risk</td>
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Stroke patients show significantly decreased selenium values

A trial by Zimmermann et al. has compared the antioxidant status of patients with acute stroke (n = 11) with patients who had suffered a stroke in the previous 12 months (n = 17). In patients with a stroke anamnesis, the average serum selenium concentration of 73.4 ± 11.1 µg/l was below the reference value of 80 µg/l selenium in serum. Values below 80 µg/l selenium in serum are considered as selenium deficit. In comparison, the serum selenium level in patients with an acute stroke showed significantly lower selenium values (61.6 ± 9.5 µg/l; p < 0.01) (Fig. 17).
Significantly reduced serum selenium concentration in patients with acute stroke

Antioxidant status in acute stroke patients and patients at stroke risk.

Fig. 17
Correlation between glutathione peroxidase concentration, neurological deficit, and outcome

Measurement of the selenium-dependent, antioxidant glutathione peroxidase displayed a significant increase of the glutathione peroxidase level in acute stroke patients on day one \( (p < 0.05) \) \((\text{Fig. 18})\). In half of the patients who had suffered a stroke in the previous 12 months, the glutathione levels were below the normal range. In contrast, the glutathione concentration in patients with an acute stroke was significantly increased \( (p < 0.01) \) \((\text{Fig. 19})\). Moreover, there was a negative correlation between the glutathione peroxidase concentration and the NIHSS (National Institute of Health Stroke Scale) at admission \( (r = -0.84; p < 0.001) \) and after seven days \( (r = -0.63; p < 0.05) \). High glutathione peroxidase concentrations correlated with a low neurological deficit (lower NIHSS value at admission) and with a favorable outcome (lower NIHSS value on day seven). These results confirmed findings acquired in animal experiments, i.e. that glutathione peroxidase can have a protective effect against brain damage and that a reduced glutathione peroxidase level is associated with increased stroke risk.\(^{[1]}\)
Significant increase of glutathione peroxidase concentration in patients with acute stroke

Antioxidant status in acute stroke patients and patients at stroke risk.

Fig. 18

Significantly increased glutathione concentration in patients with acute stroke

Antioxidant status in acute stroke patients and patients at stroke risk.

Fig. 19
Significantly reduced selenoprotein P concentration in patients with an acute stroke

In a population-based embedded case-control trial with 1,632 participants, Koyama et al. compared the serum selenium and selenoprotein P concentrations of 30 stroke patients with 30 controls. The serum selenium concentration was lower (105.2 vs 116.5 µg/l; p = 0.054) in stroke patients. The result is comparable to the Zimmermann trial. A comparison of the two studies, however, also shows that the localization of a study plays a major role in case of selenium. In Europe, the selenium levels are lower compared to Japan. Apart from the serum selenium concentration, the selenoprotein P concentration in stroke patients was significantly lower (54.5 vs. 63.9 µg/l; p = 0.006) (Table 2). A multivariate regression analysis showed that a reduced selenoprotein P level is associated with higher stroke risk (OR 0.28; 95% CI 0.1–0.85). Since the selenoprotein P concentration depends on the selenium status, it can be concluded that the markedly lower serum selenium concentrations in Europe result in lower selenoprotein P levels. Therefore the question must be posed whether a selenium-deficient diet presents an additional risk factor apart from hypertension, smoking and hypercholesterolemia for stroke.

| Significant lower serum selenium and selenoprotein P concentrations in stroke patients |
|---------------------------------|------------------------------|-----------------|
| Stroke | Control | p value |
| Selenium in serum [µg/l] | 105.2±19.6 | 116.5±16.6 | 0.054 |
| Selenoprotein P [µg/l] | 54.5±8.69 | 63.0±9.18 | 0.006 |


Table 2
Stroke patients show significantly decreased selenium values
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<td>ESPEN endorsed recommendations: Nutritional therapy in major burns[H]</td>
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*This table provides an overview. Please refer to the respective guideline for detailed information on dosage, application and conditions of use.

Products for injection therapy

**selenase® 100 µg pro injectione**

- 100 µg selenium in 2 ml solution for injection
- 10 and 50 ampoules

**selenase® T pro injectione**

- 500 µg selenium in 10 ml solution for injection
  - 2, 10, 30 (3 x 10) and 50 (5 x 10) glass vials
- 1,000 µg selenium in 20 ml solution for injection
  - 2, 10 (N2), 30 (3 x 10) and 50 (5 x 10) glass vials

Active substance: Sodium selenite pentahydrate. Prescription only

**selenase® 50 Mikrogramm Injektionslösung**

- 50 µg selenium in 1 ml solution for injection
- 10 and 50 ampoules

*selenase® 50 microgram injection solution

Active substance: Sodium selenite pentahydrate. Subject to sale in pharmacies
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**selenase®**

Active substance: Sodium selenite pentahydrate. selenase® 100 µg pro injectione, selenase® T pro injectione, selenase® 50 Mikrogramm Injektionslösung: 50 µg selenium per ml. Indications: selenase® 100 µg pro injectione, selenase® T pro injectione, selenase® 50 Mikrogramm Injektionslösung: Confirmed selenium deficiency that cannot be corrected by diet. Selenium deficiency can occur in conditions of malabsorption or malnutrition (e.g. total parenteral nutrition).

Composition:
- selenase® 100 µg pro injectione: 1 ampoule of 2 ml solution for injection contains: 0.333 mg sodium selenite pentahydrate, corresponding to 100 µg (micrograms) selenium.
- selenase® T pro injectione: 1 injection vial of 10 ml/20 ml solution for injection contains: 1.67 mg/3.33 mg sodium selenite pentahydrate, corresponding to 500 µg/1000 µg (micrograms) selenium.
- selenase® 50 Mikrogramm Injektionslösung: 1 ampoule of 1 ml solution for injection contains as active substance 0.167 mg sodium selenite pentahydrate corresponding to 50 µg selenium in an 0.9 % aqueous NaCl-solution. Excipients: Sodium chloride, hydrochloric acid, water for injections. Contra-indications: Selenium poisoning. Undesirable effects: None known to date if the medicinal product is administered according to prescription. For selenase® 100 µg pro injectione, selenase® T pro injectione, General disorders and administration site conditions: Frequency not known (cannot be estimated from the available data); after intramuscular administration local pain at the site of administration has been reported. Form of administration, size of packages:
  - selenase® 100 µg pro injectione: 10 or 50 ampoules of 2 ml solution for injection.
  - selenase® T pro injectione: 2 or 10 injection vials of 10 ml solution for injection, hospital-size pack 30 (3 × 10) or 50 (5 × 10) injection vials of 20 ml solution for injection, hospital-size pack 30 (3 × 10) or 50 (5 × 10) injection vials of 20 ml solution for injection. selenase® 50 Mikrogramm Injektionslösung: 10 and 50 ampoules respectively of 1 ml solution for injection. selenase® 100 µg pro injectione, selenase® T pro injectione: Subject to prescription. selenase® 50 Mikrogramm Injektionslösung: Subject to sale in pharmacies.
Selenium and stroke