SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Thiopental 500 mg powder for solution for injection
Thiopental 1g powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 500 mg thiopental sodium and sodium carbonate (equivalent to 470 mg thiopental sodium).
1 vial contains 1000 mg thiopental sodium and sodium carbonate (equivalent to 940 mg thiopental sodium).

Excipients with known effect:
Thiopental 500 mg powder for solution for injection contains 53 mg of sodium, i.e. 2.30 mmol of sodium in one vial.
Thiopental 1 g powder for solution for injection contains 106 mg of sodium, i.e. 4.61 mmol of sodium in one vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellowish-white powder for solution for injection

4. CLINICAL PARTICULARS

Therapeutic indications

Thiopental is used:

- For short duration anaesthesia without intubation (brief anaesthesia during surgical procedures not requiring any preparation for artificial respiration),
- For induction of general anaesthesia with or without intubation (induction of longer duration anaesthesia for surgical procedures with or without preparation for artificial respiration).

Note: As with all barbiturates, it is necessary to administer an analgesic agent when performing anaesthesia with Thiopental.

Posology and method of administration

Thiopental should only be used when qualified staff and the necessary specialist equipment for resuscitation and endotracheal intubation for the treatment of emergency medical conditions, such as respiratory failure and respiratory arrest, are available.

Posology
The dose depends on the specific sensitivity of the patient and the desired depth of anaesthesia. The following information is given solely as a guideline. Optimal efficacy can be achieved most safely by the slow repeated injection of small doses.

For the induction of general anaesthesia, the average dose for the intravenous injection is 5 mg Thiopental sodium per one kilogram of body weight. The duration of the effect is about 6 to 8 minutes. In general, 100 to 200 mg of Thiopental sodium is injected slowly over a period of 20 seconds. Any additional doses depend on the sensitivity of a respective patient and the desired depth of anaesthesia.

For short-duration anaesthesia, the total amount should not generally exceed double the sleep-inducing dose of 100 to 200 mg Thiopental sodium.

The total dose required for surgical intervention may range between 400 and 1000 mg of Thiopental sodium.

A single dose intravenous injection (approximately 3 to 4 mg sodium thiopental/kg b.w.), results in unconsciousness within 10 seconds and to anaesthesia lasting 3 – 5 minutes.

Repeat injections may be performed.
The phenomenon of acute tolerance has been demonstrated on several occasions, i.e. a higher dose may be needed after the first anaesthetically effective dose to repeat the same effect. On the other hand, if administering subsequent doses, it should be remembered that the substance accumulates.

Special Populations
Elderly
An increased effect is expected in elderly patients due to their slower metabolism. The dose should therefore be reduced accordingly

Patients with kidney or liver disease
In patients with impaired liver or kidney function, the dose is to be reduced according to the severity of the condition.

Method of Administration
For injection anaesthesia, Thiopental is dissolved in water for injection or 0.9% sodium chloride solution and subsequently slowly injected intravenously (see section 4.4).

Repeat injections may be performed. The phenomenon of acute tolerance has been observed several times; this means that a higher dose may be required after the first anaesthetically effective dose to achieve the same effect. On the other hand, the substance may accumulate after re-dosing.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Thiopental should not be used in the following cases:
- in case of known hypersensitivity to barbiturates or any excipients of Thiopental .
- acute poisoning with alcohol, sleeping pills, painkillers and psychotropic agents (medicines to treat mental/psychiatric disorders),
- hypertension, shock and status asthmaticus.

Administration of any barbiturate is contraindicated in porphyria.

Special warnings and precautions for use

Thiopental should be used in patients with caution under the following cases:
- obstructive respiratory disease (impaired breathing due to airway constriction, e.g. in bronchial asthma),
- hypovolaemia,
- severe renal and hepatic dysfunction
- anaemia
- hypothyroidism

- severe heart attack or other serious heart muscle damage,
- metabolic disorders, incl. diabetes mellitus,
- severe muscle diseases,
- in infants

There is a risk of severe hypotension in case of rapid injection (such as a bolus injection). Therefore, Thiopental should be administered slowly.

Thiopental is not approved for continuous intravenous administration. Tissue necrosis has been observed after continuous intravenous administration of Thiopental over several hours.

Thiopental inhibits the release of epinephrine (adrenaline) and reduces the effect of increased plasma renin activity.

In these cases, Thiopental may only be used if all the prerequisites in terms of staff and equipment are available to treat possible incidents, especially respiratory failure and respiratory arrest.

Application in neurological patients with increased intracranial pressure.
Thiopental has been associated with reports of severe or refractory hypokalaemia during infusion in the context; Severe rebound hyperkalaemia may occur after the end of thiopental infusion. The potential occurrence of rebound hyperkalaemia should be considered when settling the thiopental therapy.

Accidental intra-arterial and paravenous injections
Paravenous and intra-arterial injection of Thiopental solution should be absolutely avoided since the administration of Thiopental solution paravenously or intra- arterially may result in a severe tissue necrosis and resulting sequelae as well as very painful neuritis. Safe intravenous administration of Thiopental solution is imperative.

When administered paravenously, the arm should be immobilised and all efforts should be made to aspirate the previously injected solution via the indwelling cannula. The healing process may be accelerated with wet packs, possibly soaked with alcohol.

If larger volumes are injected, diffusion accelerating agents, (such as hyaluronidase), may be used. Moreover, the directly adjacent paravenous region may be infiltrated with 1% Novocain solution. In order to dilute Thiopental solution leaked into the tissue, a solution of isotonic sodium chloride should be administered subcutaneously.

Paediatric population
During procedures to diagnose disease or to treat the upper respiratory tract region, hyperreflexia (heightened reflexes) and laryngospasm (spasm of the vocal cords) can be expected, especially in children.

This medicinal product contains 53 mg per vial of Thiopental 500 mg powder for solution for injection, equivalent to 2.65% of the WHO recommended maximum daily intake of 2 g sodium for an adult, and 106 mg sodium per vial of Thiopental 1g powder for solution for injection, equivalent to 5.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interaction with other medicinal products and other forms of interaction

Thiopental is affected by other medicines as follows:
When combined with other CNS depressants (such as benzodiazepines) or with alcohol, it should be taken into account that this may produce an additive depressant effect on the central nervous system.

This also applies to central respiratory depression (opioids).

Even the substances that compete with Thiopental for plasma-protein binding, such as sulphonamides, may enhance the effect of Thiopental and lead to the reduction of the required induction dose.

Thiopental affects other medicines as follows:
If Thiopental is repeatedly used at short intervals, it should be noted that it may have an inducing effect on the liver enzymes. This may result in an accelerated breakdown of other medicines, such as coumarin derivatives, corticosteroids and oral contraceptives, and consequently reduce their effectiveness.

It will also increase methotrexate toxicity.

Incompatibilities with other medicines:
Thiopental must not be mixed with other injection or infusion solutions (exception: water for injection or 0.9 % sodium chloride solution). Furthermore, the reconstituted solution should not be administered concomitantly with other injection or infusion solutions. The solutions reconstituted with Thiopental can cause alkaline reaction and are incompatible with volume replacement solutions and acidic solutions of anaesthetic adjuvant, as this may give rise to precipitation and blockage of the injection cannula; similarly, chemical changes in the resulting solution cannot be excluded either.

Using Thiopental with food and drink
Before and even after anaesthesia, do not consume any beverages or food containing alcohol under any circumstances.

Fertility, pregnancy and lactation

Pregnancy
There is only a limited amount of data from the use of thiopental in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). In an epidemiological study in man (exposure during the first four weeks of pregnancy), no teratogenic effects could be detected. New-born babies, whose mothers had been exposed to Thiopental, showed signs and symptoms of withdrawal. Thiopental crosses the placental barrier. Therefore, a general anaesthesia with Thiopental should be in pregnant women only if clearly indicated and after a careful risk-benefit assessment.

When given during labour, new-borns should be observed for a depressive effect on breathing.

Breast feeding
Thiopental is excreted in the breast milk. The concentrations in the blood of nursing infants may be higher than in the mother because of the immature metabolic function.

Thiopental is detected in the breast milk up to 36 hours after the injection. During this time period, breastfeeding should be avoided.

Effects on ability to drive and use machines

Thiopental has a major influence on the ability to drive and use machines.

Following anaesthesia with Thiopental, the ability to respond quickly and effectively to unexpected and sudden events may be impaired. For this reason, patients should not drive a car or other vehicles following an outpatient surgical procedure. Patients should be accompanied home and drinking alcohol should be avoided under any circumstances. During this period, patients should not operate any electrical appliances or machinery, nor should they work without a firm foothold.

Undesirable effects

The frequency of possible side effects listed below are defined as:

- **very common** (≥1/10)
- **common** (<1/10 to ≥1/100)
- **uncommon** (<1/100 to ≥1/1,000)
- **rare** (<1/1,000 to ≥1/10,000)
- **very rare** (<1/10,000)
- **not known** (cannot be estimated from the available data)

Immune system disorders	Common: Allergic and pseudo-allergic reactions, for instance, brocho- and laryngospasms, erythematous and oedematous skin changes Very rare: Severe allergic reactions with anaphylactic shock and allergy-related haemolytic anaemia associated with kidney damage. Not known: anaphylactic reaction
Psychiatric disorders	Common: Psychological reactions in the form of euphoric mood (10 to 12 % incidence) and experience of dreaming (approx. 40 % incidence), also unpleasant dreams
Vascular disorders	Not known: Venous pain following the intravenous injection, thrombosis, phlebitis
Respiratory, thoracic and mediastinal disorders	Common: Hypoventilation with short-term apnoea, singultus both during spontaneous breathing and mask breathing (2 to 5% incidence, depending on the amount of medicine administered) Not known: Coughing and sneezing
Gastrointestinal disorders	Not known: Nausea and vomiting (caused by concomitant medication)
Musculoskeletal system and connective tissue	Common: Involuntary movements and muscle tremors
Renal and urinary tract	Not known: renal failure, polyuria (at high doses)
General disorders and administration site conditions	Unknown: Depending on size and venous injection site Nerve pain after intravenous injection; Thrombosis, phlebitis.
Metabolism and nutrition disorders	Unknown: hypokalaemia, hyperkalaemia

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 the national reporting system listed in Appendix V.

Overdose

The typical symptom of an overdose is a rapid drop in blood pressure, which can lead to shock. Pulmonary oedema may develop as a result of an insufficient pump function of the heart. A drop in blood pressure may also be the result of allergic reaction; but it is usually occurring in combination with allergic skin reactions.

Overdose may cause persistent respiratory insufficiency or respiratory arrest, which may be life-threatening after cessation of artificial respiration. There is a rapid drop in body temperature.

Treatment is symptomatic and should be performed under intensive-care conditions:
To maintain respiratory function, aspiration of the respiratory tract, intubation and patient ventilation are generally required. Infusion therapy with plasma volume expanders is indicated as a measure against the drop in blood pressure and for shock prophylaxis. Dopamine (2 to 5 µg/kg/min) or norepinephrine (noradrenaline 0.1 to 0.2 µg/kg/min) may be added to the solution for infusion. Body temperature must be normalised.

5 PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmaceutical group: Barbiturates, plain
ATC Code: N01AF03

Following a clinical induction dose, signs of excitation are comparatively minor. However, involuntary movements and muscle tremors may occur, depending on the dose. Thiopental causes dose-dependent suppression of the respiratory centre. Thiopental can reduce cerebral oxygen requirements and cerebral perfusion by up to 45% compared with the conscious state. These changes are evidently linked to the anaesthetic effect. In cases of increased intracranial pressure, this is reduced by thiopental after a single dose for more than 10 minutes. Intraocular pressure is also reduced. Cerebral hyperactivity, as manifested by convulsions or even visible only in the EEG, is suppressed by thiopental.

At an induction dosage of 4 mg thiopental sodium/kg BW in patients with a healthy heart, thiopental causes only a slight reduction in the mean arterial pressure. The heart rate increases by 30% and there is a very slight decrease in the maximum rate of pressure rise in the left ventricle. There is a moderate decrease in the cardiac index and stroke volume; total peripheral resistance increases by 10%. Coronary perfusion and myocardial oxygen consumption increase by the same extent, so that the arteriovenous oxygen difference remains virtually the same. These changes in general and coronary haemodynamics are negligible in patients with normal coronary reserve. Thiopental leads to a reduction in renal function. In contrast, high doses cause polyuria. Thiopental inhibits the release of epinephrine (adrenaline) and reduces the effect of increased plasma renin activity.

Pharmacokinetic properties

Distribution
A single intravenous injection (approx. 3 to 4 mg Thiopental sodium/kg BW) results in unconsciousness within 10 seconds and to anaesthesia lasting 3 to 5 minutes. Within the first minutes following the injection, 55 % of the available barbiturate is distributed into high blood flow organs.
Due to good lipid solubility, the blood-brain barrier is rapidly penetrated. Hence, the brain rapidly absorbs a considerable amount of the substance. A peak effect on the CNS can be observed after one minute. As a result of subsequent redistribution, the concentration in blood rapidly decreases and the anaesthetic effect is abolished. The half-life of the distribution phase is 8.5 min and redistribution phase is 62.7 min at a dose of 6.7 mg thiopental sodium/kg BW. Thiopental readily diffuses across the placenta and is distributed into breast milk.

Biotransformation
Thiopental is mainly metabolised in the liver by oxidation and desulphurisation. This results in a breakdown product Pentobarbital which is also hypnotically active. Thiopental is almost completely metabolised in the body to inactive metabolites with a very small percentage excreted unchanged in urine in whatever species is studied, whether human or animal. The enzymes involved in the metabolism of thiopental remain to be elucidated.

Elimination
Thiopental and its inactive metabolites are excreted primarily through the kidneys. The elimination half-life is 11.6 hours. Due to the low metabolisation rate and slow redistribution from the fatty tissue, thiopental has a relatively long residual effect. Therefore, when repeat injections are administered, the possibility of accumulation has to be considered. The indicated total dose should not be exceeded. In patients with renal insufficiency, much lower doses for induction of anaesthesia are required. In patients with uraemia or liver cirrhosis, potentiation of the effect can also be expected due to the change in the plasma proteins.

Preclinical safety data

a) Chronic toxicity
Chronic intoxication with the injection anaesthetic can be excluded due to the mode of application.

b) Mutagenic and carcinogenic potential
Thiopental has been insufficiently studied to determine its mutagenic effect. Based on previous examinations, there is no evidence for a mutagenic effect. No carcinogenicity studies have been performed.

c) Reproductive toxicology
Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings is not known.

d) Adverse reactions, not observed in clinical studies but which occurred in animals after exposure within the human therapeutic range and to be rated as possibly relevant for clinical use are:
Studies in rats demonstrated a significant increase in pulmonary oedema and resulting mortality from thiopental used concomitantly with Pentoxifyllin compared to thiopental used as monotherapy. The lethal effect was not observed when there was a time lapse between administering thiopental and Pentoxifyllin. There are no known human studies to evidence this interaction.

6 PHARMACEUTICAL PARTICULARS

List of excipients

-None

Incompatibilities

This medicine must not be mixed with other medicinal products except those mentioned in section 6.6. The solutions prepared with thiopental are strongly alkaline and are not compatible with volume replacement solutions and acidic anaesthetic adjuvant solutions, since precipitation and clogging of the injection needle may occur. Similarly, chemical changes in the added solution cannot be ruled out.

Shelf life

2 years

Shelf-life after reconstitution
Chemical and physical in-use stability after reconstitution in purified water or in 0.9% sodium chloride solution has been demonstrated for 9 hours below 25°C and 24 hours at 2 to 8°C.

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 9 hours below 25°C and 24 hours at 2 to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.
For single use after reconstitution. Discard any remainder after use.

Nature and contents of container

20 mL vials made from colourless type III glass with a rubber stopper, aluminium seal and a polypropylene blue or grey flip-off cap (blue for the 500 mg and grey for the 1 g dosage).

Special precautions for disposal and other handling

Preparing the solution for injection:
Thiopental 500 mg and 1000 mg are used for injection in a 2.5% and 5% solution.

For the 2.5% solution for injection, the contents of one Thiopental 500 mg vial are dissolved in 20 mL water for injection or 0.9% sodium chloride solution.

For the 5% solution for injection, the contents of one Thiopental 500 mg vial are dissolved in 10 mL water for injection or 0.9% sodium chloride solution.

For the 2.5% solution for injection, the contents of one Thiopental 1000 mg vial are dissolved in 40 mL water for injection or 0.9% sodium chloride solution.

For the 5% solution for injection, the contents of one Thiopental 1000 mg vial are dissolved in 20 mL water for injection or 0.9% sodium chloride solution.

Any solution of this medicine with a visible precipitate should not be administered. The solutions are used immediately after preparation.

Any unused medicinal product or waste material should be disposed of in accordance with local requirement