THIOPENTAL PANPHARMA 500 mg
THIOPENTAL PANPHARMA 1000 mg
poudre pour solution injectable

1. NAME OF THE MEDICINAL PRODUCT
THIOPENTAL PANPHARMA 500 mg powder for solution for injection
THIOPENTAL PANPHARMA 1000 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
THIOPENTAL PANPHARMA 500 mg powder for solution for injection
Each vial contains 500 mg thiopental sodium and sodium carbonate (Ph.Eur.), equivalent to 470 mg thiopental sodium.
THIOPENTAL PANPHARMA 1000 mg powder for solution for injection
Each vial contains 1000 mg thiopental sodium and sodium carbonate (Ph.Eur.), equivalent to 940 mg thiopental sodium.

3. PHARMACEUTICAL FORM
Powder for solution for injection
Yellowish-white powder

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
THIOPENTAL is used
- for short-duration anaesthesia without intubation (brief anaesthesia during surgery without preparation for artificial respiration).
- for induction of general anaesthesia with or without intubation (introduction of longer-acting anaesthesia for surgery with or without preparation for artificial respiration).

PLEASE NOTE: As with all barbiturates, it is necessary to administer an analgesic when performing anaesthesia with THIOPENTAL PANPHARMA.

4.2 Posology and method of administration
THIOPENTAL PANPHARMA may only be used if all the necessary personnel and equipment for resuscitative measures and endotracheal intubation are available to treat possible incidents, such as respiratory arrest and cardiac failure.

Posology
The dose will generally depend on the specific sensitivity of the patient and the desired depth of anaesthesia. The following information is given solely as a guideline. The optimal effect can be achieved most safely by the slow repeated injection of small doses.
For induction of general anaesthesia in adolescents and adults, the average dose for intravenous injection is 5 mg thiopental per kilogram of body weight. The duration of action is approximately 6 to 8 minutes. As a general rule, 100 to 200 mg thiopental is injected slowly over a period of 20 seconds. Every additional dose depends on the individual sensitivity of the patient and the desired depth of anaesthesia.
For short-duration anaesthesia, the total amount should generally not exceed twice the induction dose of 100 to 200 mg thiopental. The total dose required during a surgical procedure may range between 400 and 1000 mg thiopental.
A single intravenous injection (approximately 3 to 4 mg thiopental/kg BW) results in unconsciousness within 10 seconds and anaesthesia lasting 3 – 5 minutes.
Repeat injections are possible. The acute tolerance phenomenon has been observed several times, i.e. a higher dose may be required after the first anaesthetically effective dose to repeat the same effect. On the other hand, it must be remembered that the substance may accumulate if doses are repeated.

Specific patient groups
Elderly
An increased effect is expected in the elderly due to the slower redistribution of the active substance. The dose should therefore be reduced accordingly.

Patients with renal or hepatic disorders
In patients with impaired liver or kidney function or with uraemia, the dose must be reduced according to the severity of the condition.

Paediatric population
A higher thiopental dosage is usually necessary for small children due to the higher cardiac output and rapid redistribution of the active substance. The recommended dose is 3-4 mg/kg for newborns (0-27 days) and 5-8 mg/kg for infants and small children (28 days - 23 months). Children from 2 years up to 18 years usually require a higher dose per kilogram body weight than adults.

Method of administration
For injection anaesthesia, THIOPENTAL PANPHARMA is dissolved in water for injection and then slowly injected intravenously (see section 4.4).
THIOPENTAL PANPHARMA should not be used as a continuous infusion (see section 4.4).
For instructions on reconstitution of the ready-to-use solution, see section 6.6.

4.3 Contraindications
THIOPENTAL PANPHARMA must not be used in the following cases:
- known hypersensitivity to the active substance or to barbiturates
- acute intoxication with alcohol, hypnotics, analgesics and psychotropic agents
- acute hepatic porphyria, malignant hypertension
- shock
- status asthmaticus

4.4 Special warnings and precautions for use
Special care is required when using THIOPENTAL PANPHARMA in the following cases:
- obstructive airway diseases,
- hypovolaemia,
- severe kidney and liver dysfunction,
- anaemia,
- hypothyroidism,
- severe heart attack or other severe heart muscle damage,
- congestive heart failure,
- cachexia,
- severe muscle diseases,

and in infants.
If the injection is too rapid (e.g. as a bolus injection), there is a risk of a severe drop in blood pressure. Therefore, THIOPENTAL PANPHARMA must be injected slowly.
Thiopental has a dose-dependent depressant effect on the respiratory centre. Dose-dependent involuntary movements and muscle tremor may also occur.
THIOPENTAL PANPHARMA should not be administered as a continuous infusion. Tissue necrosis has been observed after continuous intravenous infusion of thiopental over several hours.
Thiopental inhibits the release of epinephrine (adrenaline) and reduces the effect of elevated plasma-renin activity.

Use in neurological patients with raised intracranial pressure
Thiopental has been associated with reports of severe or refractory hypokalaemia during infusion; severe rebound hyperkalaemia may occur after cessation of thiopental infusion. The potential for rebound hyperkalaemia should be taken into account when stopping thiopental therapy.

Accidental intra-arterial and paravenous injections:
Intra-arterial or paravenous injection must be avoided at all costs, as this may trigger severe tissue necrosis or extremely painful neuritis. In the event of paravenous injection, the arm must be immobilised and it should be attempted to aspirate the already injected solution via the indwelling cannula. Healing is accelerated by treatment with moist compresses, possibly with added alcohol. If larger amounts have been injected, agents to accelerate diffusion may be used (hyaluronidase). The directly adjacent paravenous area can also be infiltrated with 1% Novocaine solution. Isotonic sodium chloride solution should be injected subcutaneously to dilute the THIOPENTAL PANPHARMA solution that has leaked into tissues.
THIOPENTAL PANPHARMA 500 mg contains 53 mg of sodium per 500 mg vial, equivalent to 2.65 % of the WHO recommended maximum daily intake of 2 g of sodium for an adult.
THIOPENTAL PANPHARMA 1 g contains 106 mg of sodium per 1 g vial, equivalent to 5.3 % of the WHO recommended maximum daily intake of 2 g of sodium for an adult.

Paediatric population
Hyperreflexia (increased reflexes) and laryngospasm (spasm of the vocal cords) can be expected during diagnostic or therapeutic procedures of the upper airways, especially in children.

4.5 Interaction with other medicinal products and other forms of interaction
When combined with other centrally acting depressants (e.g. benzodiazepines) or with alcohol, it should be considered that this may produce additive depressant effect on the central nervous system. This also applies to central respiratory depression (opioids).
Substances competing with THIOPENTAL PANPHARMA for plasma binding such as sulphonamides may also potentiate the effect of THIOPENTAL PANPHARMA and necessitate a reduction in the required induction doses.
If THIOPENTAL PANPHARMA is administered repeatedly at short intervals, it should be noted that this may have an inducing effect on liver enzymes. This may lead to accelerated degradation of other medicinal products such as coumarin derivatives, corticosteroids, testosterone and oral contraceptives and to a reduction in their effect.
THIOPENTAL PANPHARMA increases methotrexate toxicity.

4.6 Fertility, pregnancy and lactation
Pregnancy
There is only a limited amount of data from the use of thiopental in pregnant women. Limited animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
THIOPENTAL PANPHARMA crosses the placenta. Therefore, general anaesthesia with THIOPENTAL PANPHARMA should be performed in pregnant women only if clearly indicated and following a careful benefit-risk assessment.
Following administration to women during labour, newborns should be monitored for respiratory depression.

Breast-feeding
Thiopental is excreted in human milk. Higher thiopental concentrations may be reached in the blood of the breast-fed child than in the mother due to the infant's immature metabolic performance. Thiopental can be detected in breast milk for up to 36 hours after injection. Nursing mothers should refrain from breast-feeding during this period.

4.7 Effects on ability to drive and use machines
This medicinal product has a major influence on the ability to drive and use machines.
Following anaesthesia with THIOPENTAL PANPHARMA, the ability to react quickly and appropriately to unexpected events and sudden events may be impaired for up to 24 hours. Therefore, patients should not drive a car or other vehicles after an outpatient procedure.
Patients should be accompanied home.
Patients should not use machines during this period or work without a safe hold.

4.8 Undesirable effects
Since THIOPENTAL PANPHARMA is practically always given in combination with other anaesthetic agents, it is difficult to determine which of the agents is involved in triggering undesirable effects.

The following categories are used for stating the frequency of undesirable effects:
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to <1/1,000)
Very rare (<1/10,000),
Not known (cannot be estimated from the available data).

Immune system disorders:	Common: allergic and pseudo-allergic reactions such as broncho- and laryngospasm caused by histamine release, as well as erythematous and oedematous skin changes. Very rare: severe allergic reactions such as anaphylactic shock and allergy-induced haemolytic anaemia with accompanying renal damage Frequency not known: anaphylactic reaction
Psychiatric disorders:	Very common (approximately 40% frequency): dream-like experiences, sometimes of an unpleasant nature Very common (10 to 12% frequency): mental reactions in the form of euphoric mood
Cardiac disorders:	Common: hypotension and tachycardia
Respiratory, thoracic and mediastinal disorders:	Common: hypoventilation with apnoea of short duration with short respiratory pauses Common (2-5% frequency): hiccups (depending on the dose administered both during spontaneous breathing and mask ventilation) Not known: coughing and sneezing (have been observed). Thiopental has a dose-dependent depressant effect on the respiratory centre.
Gastrointestinal disorders:	Not known: nausea and vomiting
Musculoskeletal and connective tissue disorders	Common: involuntary movements and muscle tremor
Renal and urinary disorders	Not known: renal failure, polyuria (at high dosage)
General disorders and administration site conditions:	Not known: venous pain following intravenous injection, depending on vein size and site of injection, thromboses, phlebitis.
Metabolism and nutrition disorders	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 as per local regulations.

4.9 Overdose
The typical sign of an overdose is a rapid drop in blood pressure, which may result in shock. Pulmonary oedema may develop as a result of poor pumping ability of the heart. A drop in blood pressure can also be allergy-related, in which case it mostly occurs in combination with allergic skin manifestations.
An overdose may also lead to persistent respiratory failure or respiratory arrest, which becomes life-threatening without the use of artificial respiration. There is a rapid drop in body temperature.
Treatment is symptomatic and depends on the severity of symptoms. Securing airway patency, intubation and artificial ventilation of the patient may be required, as well as stabilising the cardiovascular function with volume replacement and the addition of catecholamines.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: anaesthetics, general; barbiturates, plain.
ATC code: N01AF03
THIOPENTAL PANPHARMA is an anaesthetic belonging to the barbiturate group.
Thiopental may reduce cerebral oxygen demand and cerebral perfusion by up to 45% compared to the waking state. These changes are clearly associated with the anaesthetic effect.
A single dose of thiopental reduces increased intracranial pressure for more than 10 minutes. Intraocular pressure is also reduced. Cerebral hyperactivity, as manifested during convulsions or observable only in the EEG, is suppressed by thiopental.
At an induction dose of 4.0 mg thiopental sodium/kg BW in patients without any heart disease, thiopental causes only a slight reduction in mean arterial pressure. The heart rate increases by 30% and the maximal increase in left ventricular pressure decreases only slightly. Cardiac index and stroke volume are moderately reduced and total peripheral resistance increases by 10%. Coronary perfusion and myocardial oxygen consumption increase to the same extent, so that the difference in arteriovenous oxygen remains virtually the same. These changes in the general and coronary haemodynamics are negligible in patients with a normal coronary reserve.

5.2 Pharmacokinetic properties
Distribution
Within the first few minutes post-injection, 55% of the available barbiturate flows into highly perfused organs. Due to its excellent lipid solubility, the blood-brain barrier is rapidly penetrated. Therefore, the brain absorbs a significant amount of the substance. A maximum effect on the CNS can be observed after one minute. As a result of subsequent redistribution, concentrations rapidly decrease and the anaesthetic effect is abolished.
The half-life of the distribution phase is 9.5 minutes and the redistribution phase 62.7 minutes at a dose of 6.7 mg thiopental sodium per kilogram of body weight.
Biotransformation
Thiopental is mainly metabolised in the liver by oxidation and desulphation. This results in the degradation product, pentobarbital, which also possesses hypnotic properties.

Elimination
Thiopental and its inactive metabolites are mainly excreted via the kidneys. The elimination half-life is 11.6 hours. The residual effect of thiopental persists for a relatively long period due to its low metabolic rate and slow redistribution of the active substance from fatty tissue. Thus, the possibility of accumulation should be considered when repeated injections are given.

5.3 Preclinical safety data
Mutagenic and carcinogenic potential
Thiopental has been insufficiently studied with regard to its mutagenic potential. Based on studies to date, there are no indications of any mutagenic effect. No carcinogenicity studies have been performed to date.

Toxicity to reproduction
No teratogenic effects were demonstrated in studies on rodents.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None.

6.2 Incompatibilities
THIOPENTAL PANPHARMA must not be mixed with other solutions for injection and infusion (except those medicinal products mentioned above and 0.9% sodium chloride solution). The solutions prepared with THIOPENTAL PANPHARMA react alkaline and are not compatible with volume replacement solutions and acidic solutions used as an adjuvant in anaesthesia, since precipitation and clogging of the injection needle may occur. Similarly, chemical changes in the prepared solution cannot be ruled out.

6.3 Shelf life
3 years

Shelf-life after reconstitution
Chemical and physical stability of the ready-to-use solution has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, the ready-to-use preparation should be used immediately.
If the ready-to-use solution is not used immediately, storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage
Do not store above 25°C.
Keep the vials in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
Powder in vials.
Pack sizes: Box of 5 / 10 / 25 / 50 or 100 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Preparing the solution for injection:
THIOPENTAL PANPHARMA 500 mg is used for injection in a 2.5% and 5% solution.
For the 2.5% solution for injection, the contents of one THIOPENTAL PANPHARMA 500 mg vial are dissolved in 20 mL water for injection.
For the 5% solution for injection, the contents of one THIOPENTAL PANPHARMA 500 mg vial are dissolved in 10 mL water for injection.

THIOPENTAL PANPHARMA 1000 mg is used for injection in a 5% solution.
For this concentration, the contents of one THIOPENTAL PANPHARMA 1000 mg vial are dissolved in 20 mL water for injection.
The following instructions must be strictly complied with when preparing the solution for injection:
The corresponding quantity of water for injection should be injected into the vial so that the solvent causes the substance to swirl vigorously. Otherwise, the substance may clump together and the dissolution process could be delayed. If this is the case, complete dissolution of the substance can still be achieved by repeated withdrawal and vigorous re-injection into the vial.
After the substance has been dissolved, undissolved particles of between 7 and 350 µm may be detected in isolated cases with a magnifying glass under normal daylight conditions. These are aggregates of extremely fine substance crystals. These particles do not affect the efficacy and tolerability of the product.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
PANPHARMA
10 rue du Chenôt
Parc d'activité du Chenôt
56380 BEIGNON - FRANCE

8. DATE OF REVISION OF THE TEXT

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Medicine for hospital prescription.

GROUPE PANPHARMA
ROTEXMEDICA GmbH PANPHARMA S.A.

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