SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Thiopental VUAB inj.plv.sol. 0,5 g
Thiopental VUAB inj.plv.sol. 1,0 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Thiopental VUAB inj.plv.sol. 0,5 g: Thiopental sodium and sodium carbonate 500 mg in one vial
Thiopental VUAB inj.plv.sol. 1,0 g: Thiopental sodium and sodium carbonate 1000 mg in one vial

3. PHARMACEUTICAL FORM

Powder for injection solution
Yellowish powder

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Thiopental is indicated:
- as the sole anesthetic agent for brief (15 minute) surgery procedures,
- for induction of anesthesia prior to administration of other anesthetic agents,
- to supplement regional anesthesia,
- to provide hypnosis during balanced anesthesia with other agents for analgesia or muscle relaxation,
- for the control of convulsive states during or following inhalation anesthesia, local anesthesia, or other causes,
- in neurosurgical patients with increased intracranial pressure, if adequate ventilation is provided,
- for narcoanalysis and narcosynthesis in psychiatric disorders.

4.2. Posology and method of administration

Using of Thiopental is reserved only for specialist in anesthesia.

Preparation of solutions
Thiopental VUAB inj.plv.sol. is supplied as a yellowish, hygroscopic powder in a vial. Solutions should be prepared aseptically with one of the three following diluents:
- Sterile Water for Injection (according Ph.Eur.),
- solution for infusion of sodium chloride (9 mg/l),
- 5% dextrose solution for infusion.

Clinical concentrations used for intermittent intravenous administration vary between 2.0% and 5.0%. A 2.0% or 2.5% solution is most commonly used. A 3.4% concentration in sterile water for injection is isotonic; concentrations less than 2.0% in this diluent are not used because they cause hemolysis. For continuous intravenous drip administration, concentrations of 0.2% or 0.4% are used. Solutions may be prepared by adding thiopental to 5% water solution of dextrose or to 0.9% solution of sodium chloride.

CALCULATIONS FOR VARIOUS CONCENTRATIONS
Since Thiopental contains no added bacteriostatic agent, extreme care in preparation and handling should be exercised at all times to prevent the introduction of microbial contaminants. Solutions should be freshly prepared and used promptly; when reconstituted for administration to several patients; unused portions should be discarded after 24 hours. Sterilization by heating should not be attempted.

Thiopental VUAB is administered by the intravenous route only.

Individual response to the drug is so varied that there can be no fixed dosage. The drug should be titrated against patient requirements as governed by age, sex and body weight. Younger patients require relatively larger doses than middleaged and elderly persons; the latter metabolize the drug more slowly.

Pre-puberty requirements are the same for both sexes, but adult females require less than adult males.

Dose is usually proportional to body weight and obese patients require a larger dose than relatively lean persons of the same weight.

### Premedication

Premedication usually consists of atropine or scopolamine to suppress vagal reflexes and inhibit secretions. In addition, a barbiturate or an opiate is often given. Barbiturates (f.e. phenobarbital, pentobarbital) have sedative anticonvulsive effect, but none analgesic effect.

#### Dosage of pentobarbital

**Adults:** 120 mg.

**Children:**
- 0 to 6 months = 0 mg
- 6 months to 3 years = 15 to 30 mg
- 3 to 18 years = 30 to 120 mg.

Opiates (alkaloid of opium or synthetic derivates of morphine) are sedatives and generally are analgesic.

**Dosage of morphine:** Adults = 10 to 15 mg, elderly = 3 mg.

### Test Dose

It is advisable to inject i.v. a small “test” dose of 25 to 75 mg (1 to 3 ml of a 2.5% solution) to assess tolerance or unusual sensitivity to thiopental and pausing to observe patient reaction for at least 60 seconds. If unexpectedly deep anesthesia develops or if respiratory depression occurs, consider these possibilities:

1. The patient may be unusually sensitive to thiopental.
2. The solution may be more concentrated than had been assumed.
3. The patient may have received too much premedication.

### Use in Anesthesia

Moderately slow induction can usually be accomplished in the “average” adult by injection of 50 to 75 mg of thiopental at intervals of 20 to 40 seconds, depending on the reaction of the patient. Once anesthesia is established, additional injections of 25 to 50 mg can be given whenever the patient

<table>
<thead>
<tr>
<th>Desired concentration</th>
<th>Amounts to Use</th>
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</thead>
<tbody>
<tr>
<td>% mg/ml g of Thiopental ml of diluent</td>
<td></td>
</tr>
<tr>
<td>0.2 2 1 500</td>
<td></td>
</tr>
<tr>
<td>0.4 4 1 250</td>
<td></td>
</tr>
<tr>
<td>2.0 20 5 250</td>
<td></td>
</tr>
<tr>
<td>2.5 25 10 500</td>
<td></td>
</tr>
<tr>
<td>5.0 50 1 40</td>
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<tr>
<td>500 200</td>
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<td>100 100</td>
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</tbody>
</table>
moves. Slow injection is recommended to minimize respiratory depression and the possibility of overdosage.

The smallest dose consistent with attaining the surgical objective is the desired goal. Momentary apnea following each injection is typical, and progressive decrease in the amplitude of respiration appears with increasing dosage. Pulse remains normal or increases slightly and returns to normal. Muscles usually relax about 30 seconds after unconsciousness is attained, but this may be masked if a skeletal muscle relaxant is used. The tone of jaw muscles is a fairly reliable index. The pupils may dilate but later contract. Sensitivity to light is not usually lost until a level of anesthesia deep enough to permit surgery is attained. Nystagmus and divergent strabismus are characteristic during early stages, but at the level of surgical anesthesia, the eyes are central and fixed. Corneal and conjunctival reflexes disappear during surgical anesthesia.

When thiopental is used for induction in balanced anesthesia with a skeletal muscle relaxant and an inhalation agent, the total dose of thiopental can be estimated and then injected in two to four fractional doses. With this technique, brief periods of apnea may occur which may require assisted or controlled pulmonary ventilation.

When thiopental is used as the sole anesthetic agent, the desired level of anesthesia can be maintained by injection of small repeated doses as needed or by using a continuous intravenous drip in a 0.2% or 0.4% concentration. (Sterile water should not be used as the diluent in these concentrations, since hemolysis will occur.) With continuous drip, the depth of anesthesia is controlled by adjusting the rate of infusion. Usual dose is 100 to 150 mg of thiopental administered in 10-15s. If necessary, dose 100 – 150 mg is repeated after 1 minute. The average dose for adult with weight of 70 kg is 200 – 300 mg, maximum 500 mg. In children is used dose of 2 – 7 mg/kg; total dose must not cross 7 mg/kg.

**Use in Convulsive States**

For the control of convulsive states following anesthesia (inhalation or local) or other causes, 75 to 125 mg should be given as soon as possible after the convulsion begins. Convulsions following the use of a total anesthetic may require 125 to 250 mg of thiopental given over a ten minute period. If the convulsion is caused by a local anesthetic, the required dose of thiopental will depend upon the amount of local anesthetic given and its convulsant properties. In children is used dose 2 – 3 mg/kg.

**Use in Neurosurgical Patients with Increased Intracranial Pressure**

In neurosurgical patients, intermittent bolus injections of 1.5 to 3.5 mg/kg of body weight may be given to reduce elevations of intracranial pressure, if adequate ventilation is provided. 2% solution of thiopental is recommended in convulsion states and for neurosurgical use, because causes lower respiratory and circulatory depression. In children is used dose 1,5 – 5 mg/kg.

**Use in Psychiatric Disorders**

For narcoanalysis and narcosynthesis in psychiatric disorders, premedication with an anticholinergic agent may precede administration of thiopental. After a test dose, thiopental is injected at a slow rate of 100 mg/min with the patient counting backwards from 100. Shortly after counting becomes confused but before actual sleep is produced, the injection is discontinued. Allow the patient to return to a semidrowsy state where conversation is coherent. Alternatively, thiopental may be administered by rapid i.v. drip using a 0.2% concentration in 5% dextrose and water. At this concentration, the rate of administration should not exceed 50 ml/min. In children is not known using in this indication.

**Hepatic function**

It is known, that thiopental administered in normal doses does not decrease hepatic function. Disorder of liver occurs after high crossing of recommended doses or in case of associated hypoxia. In these conditions is reduced reserve of glycogen in liver, prothrombin time is prolonged, bilirubunaemia is
increased. Hepatitis with damaging cells reduces excretion of anesthetic and must be used fractionation and reduction of administered doses.

**Renal function**
Diuresis is slightly decreased, but toxic effect on kidney is insignificant. In azotaemic patients is excretion slightly slowed.

### 4.3. Contraindication

Absence of suitable veins for intravenous administration.  
Acute intermittent porphyria.  
Hypersensitivity to thiopental, barbiturates or any excipient

### 4.4. Special warnings and precautions for use

Keep resuscitative and endotracheal intubation equipment and oxygen readily available. Maintain patency of the airway at all times.  
This drug should be administered only by persons qualified in the use of intravenous anesthetics.

Caution must be used in patients with hypotension or under conditions in which the hypnotic effect may be prolonged or potentiated, as in case of hepatic or renal dysfunction.

Avoid extravasation or intra-arterial injection. If used in conditions involving relative contraindications reduce dosage and administer slowly.

Observe aseptic precautions at all times in preparation and handling of Thiopental VUAB inj.plv.sol. solutions.

Care should be taken in administering the drug to patients with advanced cardiac disease, increased intracranial pressure, asthma, myasthenia gravis, endocrine insufficiency and/or hyperfunction (pituitary, thyroid, adrenal, pancreas) and incompetence of valve.

As other barbiturates, using of thiopental may cause addiction.

Relative Contraindications:  
- Severe cardiovascular disease  
- Hypotension or shock  
- Conditions in which the hypnotic effect may be prolonged or potentiated (excessive premedication, Addison’s disease, hepatic or renal dysfunction, myxedema, increased blood urea, severe anemia, asthma, myasthenia gravis)  
- Endocrine insufficiency  
- Increased intracranial pressure  
- Ophthalmoplegia  
- Decreased respiratory functions, obstruction of airways  
- Angina Ludovici, sepsis  
- Obesity

### 4.5 Interaction with other medicinal products and other forms of interaction

Following interactions were observe with Thiopental:

Aminophylline: Thiopental antagonism  
Diazoxide: Hypotension  
Midazolam: Synergism  
Opioid analgesics: Decreased sensibility to pain  
Probenecid: Prolonged action of thiopental
Metoclopramide: Increased hypnotic effect of thiopental.

4.6. Pregnancy and lactation

Animal reproduction studies have not been conducted with thiopental. Thiopental crosses the placental barrier. Thiopental should be given to a pregnant woman only if clearly needed.

Thiopental is excreted to milk; breastfeeding must be stop for 24 hours following after using thiopental.

4.7. Effects on ability to drive and use machines

Patients must not drive and use machine, it is dangerous. These activities are possible after 24 hours after application.

4.8. Undesirable effects

The frequencies of adverse events are ranked according to the following:
Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100, rare (≥1/10,000, <1/1000) and very rare (<1/10,000).

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th>Common: bradycardia, hypotension, arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorder</td>
<td>Common: respiratory depression, bronchospasm, laryngospasm, coughing</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common: cold/shivering, Rare: anaphylactoid reactions</td>
</tr>
</tbody>
</table>

4.9. Overdose

Overdosage may occur from too rapid or repeated injections. Too rapid injection may be followed by an alarming fall in blood pressure. Apnea, occasional laryngospasm, coughing and other respiratory difficulties with excessive or too rapid injections may occur.
Cardiovascular collapse can occur, treatment must restore fall in blood with suitable measure: volume expansion and/or vasopresors.
In the event of suspected or apparent overdosage, the drug should be discontinued, a patent airway established (intubate if necessary) or maintained, and oxygen should be administered, with assisted ventilation if necessary.

Respiratory depression (hypoventilation, apnea)
Respiratory depression may result from either unusual responsiveness to thiopental or overdosage, is managed as stated above. Thiopental should be considered to have the same potential for producing respiratory depression as an inhalation agent, and patency of the airway must be protected at all times.

Laryngospasm
Laryngospasm may occur with light thiopental narcosis, at intubation, or in the absence of intubation if foreign matter or secretions in the respiratory tract create irritation. Laryngeal and bronchial vagal reflexes can be suppressed, and secretions minimized by giving atropine or scopolamine premedication and a barbiturate or opiate. Barbiturates (f.e. phenobarbital, pentobarbital) have sedative anticonvulsive effect, but none analgesic effect.

Dosage of pentobarbital
Adults: 120 mg.
Children: 0 to 6 months = 0 mg
6 months to 3 years = 15 to 30 mg
3 to 18 years = 30 to 120 mg.

Opiates (alkaloid of opium or synthetic derivates of morphine)
Dosage: Adults = 10 to 15 mg, elderly = 3 mg.

Use of a skeletal muscle relaxant or positive pressure oxygen will usually relieve laryngospasm. Tracheostomy may be indicated in difficult cases.

**Myocardial depression**
Myocardial depression, proportional to the amount of drug in direct contact with the heart, can occur and may cause hypotension, particularly in patients with an unhealthy myocardium. Arrhythmias may appear if pCO2 is elevated, but they are uncommon with adequate ventilation. Management of myocardial depression is the same as for overdosage. Thiopental does not sensitize the heart to epinephrine or other sympathomimetic amines.

**Extravascular infiltration**
Extravascular infiltration should be avoided. Care should be taken to insure that the needle is within the lumen of the vein before injection of thiopental. Extravascular injection may cause chemical irritation of the tissues varying from slight tenderness to venospasm, extensive necrosis and sloughing. This is due primarily to the high alkaline pH (10 to 11) of clinical concentrations of the drug. If extravasation occurs, the local irritant effects can be reduced by injection of 1% procaine locally to relieve pain and enhance vasodilatation. Local application of heat also may help to increase local circulation and removal of the infiltrate.

**Intra-arterial injection**
Intra-arterial injection can occur inadvertently, especially if an aberrant superficial artery is present at the medial aspect of the antecubital fossa. The area selected for intravenous injection of the drug should be palpated for detection of an underlying pulsating vessel. Accidental intra-arterial injection can cause arteriospasm and severe pain along the course of the artery with blanching of the arm and fingers. Appropriate corrective measures should be instituted promptly to avoid possible development of gangrene. Any patient complaint of pain warrants stopping the injection. Methods suggested for dealing with this complication vary with the severity of symptoms. The following have been suggested:
1. Dilute the injected thiopental by removing the tourniquet and any restrictive garments.
2. Leave the needle in place, if possible.
3. Inject the artery with a dilute solution of papaverine (40 to 80 mg), or 10 ml of 1% procaine, to inhibit smooth muscle spasm.
4. If necessary, perform sympathetic block of the brachial plexus and/or stellate ganglion to relieve pain and assist in opening collateral circulation. Papaverine can be injected into the subclavian artery, if desired.
5. Unless otherwise contraindicated, institute immediate heparinization to prevent thrombus formation.
6. Consider local infiltration of an alpha-adrenergic blocking agent such as phentolamine into the vasospastic area.
7. Provide additional symptomatic treatment as required.

**Shivering**
Shivering after thiopental anesthesia, manifested by twitching face muscles and occasional progression to tremors of the arms, head, shoulder and body, is a thermal reaction due to increased sensitivity to cold. Shivering appears if the room environment is cold and if a large ventilatory heat loss has been sustained with balanced inhalation anesthesia employing nitrous oxide. Treatment consists of warming the patient with blankets, maintaining room temperature near 22° C and administration of chlorpromazine or methylphenidate.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: NO1AF03

Thiopental is a thiobarbiturate, the sulfur analogue of urea. Thiopental is an ultrashort-acting depressant of the central nervous system which induces hypnosis and anesthesia, but not analgesia. It crosses haemato-encephalic barrier and dept of anesthesia depends on dose. Thiopental produces hypnosis within 30 to 40 seconds of intravenous injection. Recovery after a small dose is rapid, with some somnolence and retrograde amnesia.

5.2. Pharmacokinetic properties

Absorption
Thiopental acts immediately after application of injection. Dose of 3 – 4 mg/kg of thiopental induce loss of consciousness. Induction time of injection application is 30 – 40 s.

Distribution
Concentration in spinal fluid is slightly less than in the plasma. The distribution and fate of thiopental (as with other barbiturates) is influenced chiefly by its lipid solubility (partition coefficient), protein binding and extent of ionization. Thiopental has a partition coefficient of 580. Approximately 80% of the drug in the blood is bound to plasma protein. Repeated intravenous doses lead to prolonged anesthesia because fatty tissues act as a reservoir; they accumulate thiopental in concentrations 6 to 12 times greater than the plasma concentration, and then release the drug slowly to cause prolonged anesthesia.

Biotransformation
Thiopental is largely degraded in the liver and to a smaller extent in other tissues, especially the kidney and brain. It has a pKa of 7.4. Biotransformation products of thiopental are pharmacologically inactive and mostly excreted in the urine.

Elimination
The half-life of the elimination phase after a single intravenous dose is three to eight hours.

5.3. Preclinical safety data

No test on mutagenic a carcinogenic potential were not done, but risk is insignificant.

Teratogenic potential of thiopental was proved.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None.

6.2. Incompatibilities
Any solution of Thiopental VUAB inj.plv.sol., with a visible precipitate should not be administered. The stability of Thiopental VUAB inj.plv.sol. solutions depends upon several factors, including the diluent, temperature of storage and the amount of carbon dioxide from room air that gains access to the solution. Any factor or condition which tends to lower pH (increase acidity) of Thiopental VUAB inj.plv.sol. solutions will increase the likelihood of precipitation of thiopental acid. Such factors include the use of diluents which are too acidic and the absorption of carbon dioxide which can combine with water to form carbonic acid. Solutions of suxamethonium, tubocurarine or other drugs which have an acid pH should not be mixed with Thiopental VUAB inj.plv.sol. solutions. The most stable solutions are those reconstituted in water and/or isotonic saline and/or solution of dextrose, kept under refrigeration and tightly stoppered. The presence or absence of a visible precipitate offers a practical guide to the physical compatibility of prepared solutions of Thiopental VUAB inj.plv.sol.

6.3. Shelf life

Before first opening: 3 years
After reconstitution: 24 hours

6.4. Special precautions for storage

Before first opening: The medicinal product does not require any special storage conditions.
After reconstitution: Store in refrigerator (2 – 8°C).

Do not use Thiopental VUAB inj.plv.sol. after the expiry date which is stated on packaging material. The expiry date refers to the last day of that month.

Solutions of Thiopental VUAB inj.plv.sol. must be prepared fresh and must be used rapidly. Solution unused in 24 hours must be disposed. Prepared solutions must not be sterilised with vapour.

6.5. Nature and contents of container

Pure glass (hydrolytic class I or II) vial with rubber stopper, aluminium seal, box.

Thiopental VUAB inj.plv.sol. 0,5 g: 1 vial
Thiopental VUAB inj.plv.sol. 1,0 g: 1 vial

6.6. Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

VUAB Pharma a.s.
Vltavská 53
25263 Roztoky
Czech Republic

8. MARKETING AUTHORISATION NUMBER

Thiopental VUAB inj.plv.sol. 0,5 g: 05/167/09-C
Thiopental VUAB inj.plv.sol. 1,0 g: 05/168/09-C
9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
18.2.2009

10. DATE OF REVISION OF THE TEXT.
18.2.2009