PENTOTHAL FOR INJECTION

NAME OF THE MEDICINE
Thiopental Sodium

DESCRIPTION
Chemical name: sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate.
Thiopental sodium is a thiobarbiturate, the sulfur analogue of pentobarbitone sodium. It has a pKa of 7.4.

\[
\begin{align*}
\text{S} & \quad \text{Na} \\
\text{H} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{C}
\end{align*}
\]

The empirical formula of thiopental sodium is \( C_{11}H_{17}N_{2}NaO_{2}S \) and its molecular weight is 264.32.
CAS Number: 71-73-8

Thiopental sodium is a yellowish hygroscopic powder stabilised with anhydrous sodium carbonate 60 mg/g thiopental sodium.

PHARMACOLOGY
Pharmacodynamics
Thiopental sodium is an ultrashort acting depressant of the central nervous system which induces hypnosis and anaesthesia, but not analgesia. It produces hypnosis within 30 to 40 seconds of intravenous injection. Consciousness returns after 20 to 30 minutes of a single induction dose. Recovery after a small dose is rapid, with some somnolence and retrograde amnesia.
The mechanism by which barbiturate anaesthetics produce general anaesthesia is not completely understood. It has been proposed that they act by enhancing responses to gamma-aminobutyric acid (GABA), diminishing glutamate responses, and directly depressing excitability by increasing membrane conductance, thereby producing a net decrease in neuronal excitability to provide anaesthetic action.
As sedative hypnotics, the barbiturates appear to act at the level of the thalamus where they inhibit ascending conduction in the reticular formation, thus interfering with the transmission of impulses to the cortex. Thiopental sodium reduces intracranial pressure. It has a dose related depression of respiratory and laryngeal reflexes.
Thiopental sodium depresses the myocardium and cardiac output decreases as the plasma concentration of the drug rises. Cardiac irritability is unaffected. Respiration is markedly depressed by thiopental sodium. Following a few deep breaths, a short period of apnoea is common, respiration being resumed with a diminished rate and depth. The degree of respiratory depression depends on the dose of thiopental sodium administered and the speed of administration. Thiopental sodium may decrease lower oesophageal sphincter tone. Patients may experience a taste sensation of garlic after thiopental sodium is administered but before the onset of anaesthesia.

**Pharmacokinetics**
Repeate intravenous doses lead to prolonged anaesthesia because fatty tissues act as a reservoir. They accumulate thiopental sodium in concentrations 6 to 12 times greater than the plasma concentration and then release the drug slowly to cause prolonged anaesthesia. The half-life of the elimination phase after a single intravenous dose is three to eight hours. The distribution and fate of thiopental sodium (as with other barbiturates) is influenced chiefly by its lipid solubility (partition coefficient), protein binding and extent of ionisation. Thiopental sodium has a partition coefficient of 580. Approximately 80% of the drug in the blood is bound to plasma protein. Thiopental sodium is largely degraded in the liver and to a smaller extent in other tissues, especially the kidneys and brain. Concentration in spinal fluid is slightly less than in the plasma. Biotransformation products of thiopental sodium are pharmacologically inactive and mostly excreted in the urine. Barbiturates may precipitate acute porphyria in susceptible patients by enhancing porphyrin synthesis.

**INDICATIONS**
- As the sole anaesthetic agent for brief surgical procedures.
- Induction of anaesthesia prior to the administration of other anaesthetic agents.
- Short-term control of convulsive states.
- Supplement to regional anaesthesia or low potency agents such as nitrous oxide.

**CONTRAINDICATIONS**
**Absolute:**
- Complete absence of suitable veins
- Allergy or hypersensitivity to barbiturates
- Status asthmaticus or when an adequate airway cannot be maintained during operation
- Latent or manifest porphyria
• Constrictive pericarditis
• Severe respiratory embarrassment
• Variegate or acute intermittent porphyria
• Inflammatory conditions of the mouth, jaw and neck

Relative:
• Severe cardiovascular disease, hypotension or shock, and conditions in which the hypnotic effect may be prolonged or potentiated i.e. excessive premedication
• Addison's disease
• Hepatic or renal dysfunction
• Myxoedema
• Increased blood urea
• Severe anaemia
• Myasthenia gravis

PRECAUTIONS
This medicine should be administered only by persons qualified in the use of intravenous anaesthetics. A person competent in anaesthesia management should be in constant attendance and adequate facilities for support of respiration and circulation should be available when thiopental sodium for injection is being used.

Avoid extravasation or intra-arterial injection.

Thiopental sodium for injection should be administered with caution to patients with pre-existing hypotension or in conditions where the hypnotic effect may be prolonged or intensified, such as in the presence of hepatic disease and renal disease.

Respiratory depression may result from either an unusual responsiveness to thiopental sodium or an overdosage. Therefore, it should not be administered without the ready availability of resuscitative equipment including that necessary for endotracheal intubation. In this regard, thiopental sodium should be considered to have the same potential as an inhalation anaesthetic, and patency of the airway must be protected at all times.

Observe aseptic precautions at all times in the preparation and handling of thiopental sodium solutions.
Special care should be exercised under the following circumstances; if used in these conditions reduce the dose and administer slowly.

Moderate degree of hypotension from any cause including shock.

Conditions in which the hypnotic effect will be prolonged: excessive premedication, hepatic and renal dysfunction, increased blood urea, severe anaemia, Addison's disease and myxoedema.

Severe cardiovascular disease including peripheral circulatory failure, also increased intracranial pressure, asthma, myasthenia gravis, severe uraemia, endocrine insufficiency (pituitary, thyroid, adrenal, pancreas), muscular dystrophies and myotonias.

Debilitated patients.

**Use in the elderly**

Following administration of barbiturate anaesthetics to elderly patients for short (outpatient) procedures, recovery of cognitive and psychomotor functions is generally slower than in younger patients. The percentage of plasma bound drug decreases and the volume of distribution and half-life increase in the aged patient. Elderly patients are also more likely to have age related hepatic function impairment, which may require reduction of dosage in patients receiving barbiturate anaesthetics.

**Use in pregnancy (Category A)**

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Thiopental sodium readily crosses the placental barrier. The concentration in cord vein blood is at its maximum two to three minutes after an intravenous dose is administered to the mother. The fetal blood level is related to maternal blood level but is considerably lower. Animal reproduction studies have not been conducted with thiopental sodium. It is also not known whether thiopental sodium can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Thiopental sodium should be given to a pregnant woman only if clearly needed.

**Use in lactation**

Small amounts of thiopental sodium may appear in the milk of breastfeeding mothers following administration of large doses.
Paediatric use
Appropriate studies on the relationship of age to the effects of barbiturate anaesthetics have not been performed in the paediatric population. Paediatric populations have demonstrated a lower percentage protein binding than in adults. The half-life may be increased in the neonate. No paediatric specific problems have been documented to date.

INTERACTIONS WITH OTHER MEDICINES
Table 1 lists the effects of interactions between Pentothal for Injection and other medicines.

Table 1. Pentothal for Injection Interactions with other medicines

<table>
<thead>
<tr>
<th>Medicines</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probenecid</td>
<td>Prolonged action of thiopental sodium</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Decreased antinociceptive action</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Thiopental sodium antagonism</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Synergism</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Increased depressant and hypotensive effect</td>
</tr>
<tr>
<td>CNS depressant medications</td>
<td>Increased depressant and hypotensive effect</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Additive hypotensive effect</td>
</tr>
<tr>
<td>Hypotension producing medications</td>
<td>Additive hypotensive effect</td>
</tr>
<tr>
<td>Ketamine (especially in high doses or when rapidly administered)</td>
<td>Increased risk of hypotension and/or respiratory depression</td>
</tr>
<tr>
<td>Magnesium sulfate (parenteral)</td>
<td>May increase CNS depressant effects</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>May potentiate hypotensive and CNS excitatory effects of barbiturate anaesthetics</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>Reduce thiopental sodium dosage requirements</td>
</tr>
</tbody>
</table>

Effect on laboratory tests
Thiopental sodium may decrease thyroid uptake of sodium iodide (I123 and I131) and sodium pertechnetate (Tc99m).

Effect on ability to drive or operate machinery
Patients should be advised of possible adverse effects on their ability to drive or perform other tasks requiring alertness and coordination. Impairment of psychomotor skills may occur following barbiturate anaesthesia and may persist
for varying lengths of time (usually about 24 hours) depending upon the anaesthetic and/or combination of medications used and the total dosages administered.

**ADVERSE EFFECTS**
Hypersensitivity reactions to barbiturates including thiopental sodium have been reported.

Adverse effects include respiratory depression, myocardial depression, cardiac arrhythmias, prolonged somnolence and recovery, hypotension, tachycardia, sneezing, coughing, bronchospasm, laryngospasm and shivering.

Anaphylactoid reactions to thiopental sodium have been reported. Symptoms, e.g. urticaria, bronchospasm, vasodilatation and oedema, should be managed by conventional means.

Excitatory phenomena such as involuntary muscle movements, coughing and hiccups have been reported.

Rarely, immune haemolytic anaemia with renal failure and radial nerve palsy have been reported.

**DOSAGE AND ADMINISTRATION**
Pentothal for Injection 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 bodyweight. Younger patients require relatively larger doses than middle aged and elderly people; the latter metabolise the drug more slowly. Prepuberty requirements are the same for both sexes, but adult females require less than adult males. Dose is usually proportional to bodyweight and obese patients require a larger dose than relatively lean people of the same weight.

The use of a continuous infusion increases the likelihood of overdosage, with a subsequent prolonged recovery period. Cloudy solutions or solutions showing a precipitate should not be administered.

**Premedication**
Premedication usually consists of atropine or hyoscine to suppress vagal reflexes and inhibit secretions. Ideally, the peak effect of these medications should be reached shortly before the time of induction.
**Test dose**
It is advisable to inject a small test dose of Pentothal for Injection 25 to 75 mg (1 to 3 mL of a 25 mg/mL solution) to assess tolerance or unusual sensitivity to Pentothal for Injection, and pause to observe patient reaction for at least 60 seconds.

If unexpectedly deep anaesthesia develops or if respiratory depression occurs, consider these possibilities:
the patient may be unusually sensitive to Pentothal for Injection;
the solution may be more concentrated than had been assumed;
or the patient may have received too much premedication.

**Use in anaesthesia**
Moderately slow induction can usually be accomplished in the average adult by injection of 50 to 75 mg (2 to 3 mL of a 25 mg/mL solution) at intervals of 20 to 40 seconds, depending on the reaction of the patient. Once anaesthesia is established, additional injections of 25 to 50 mg can be given whenever the patient needs. Slow injections are recommended to minimise respiratory depression and the possibility of overdosage. The smallest dose consistent with attaining the surgical objective is the desired goal. Momentary apnoea following each injection is typical, and a 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 anaesthesia deep enough to permit surgery is attained. Nystagmus and divergent strabismus are characteristic during early stages, but at the level of surgical anaesthesia, the eyes are central and fixed. Corneal and conjunctival reflexes disappear during surgical anaesthesia. When Pentothal for Injection is used for induction in balanced anaesthesia with a skeletal muscle relaxant and an inhalation agent, the total dose of Pentothal for Injection can be estimated and then injected in two to four fractional doses. With this technique, brief periods of apnoea may occur which may require assisted or controlled pulmonary ventilation. As an initial dose, Pentothal for Injection 210 to 280 mg (3 to 4 mg/kg) is usually required for rapid induction in the average adult (70 kg). When Pentothal for Injection is used as the sole anaesthetic agent, the desired level of anaesthesia can be maintained by injection of small repeated doses as needed or by using a continuous intravenous drip in a 2 or 4 mg/mL concentration. (Sterile water should not be used as the diluent in these concentrations, since
haemolysis will occur.) With a continuous drip, the depth of anaesthesia is controlled by adjusting the rate of infusion.

**Use in convulsive states**
For the control of convulsive states following anaesthesia (inhalation or local) or other causes, 75 to 125 mg (3 to 5 mL of a 25 mg/mL solution) should be given as soon as possible after the convulsion begins. Convulsions following the use of a local anaesthetic may require Pentothal for Injection 125 to 250 mg given over a ten minute period. If the convulsion is caused by a local anaesthetic, the required dose of thiopental sodium will depend upon the amount of local anaesthetic given and its convulsant properties.

**Use in neurosurgical patients with increased intracranial pressure**
In neurosurgical patients, intermittent bolus injections of 1.5 to 3.5 mg/kg bodyweight may be given to reduce intraoperative elevations of intracranial pressure if adequate ventilation is provided.

**Management of some complications**
Respiratory depression (hypoventilation, apnoea), which may result from either unusual responsiveness to Pentothal for Injection or overdosage, is managed as stated above. Pentothal for Injection 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 may occur with light Pentothal for Injection 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 minimised by giving atropine or hyoscine premedication and a barbiturate or opiate. Use of a skeletal muscle relaxant or positive pressure oxygen will usually relieve laryngospasm. Tracheostomy may be indicated in difficult cases.

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. Pentothal for Injection does not sensitise the heart to adrenaline or other sympathomimetic amines.
Extravascular infiltration should be avoided. Care should be taken to ensure that the needle is within the lumen of the vein before injection of Pentothal for Injection. 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 procaine (2%) 20 mg/mL 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 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. Dilute the injection of Pentothal for Injection by removing the tourniquet and any restrictive garments. Leave the needle in place, if possible. Inject the artery with a dilute solution of papaverine 40 to 80 mg or 5 mL of procaine (2%) 20 mg/mL, to inhibit smooth muscle spasm. 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. Unless otherwise contraindicated, institute immediate heparinisation to prevent thrombus formation. Consider local infiltration of an alpha-adrenergic blocking agent such as phentolamine into the vasospastic area. Provide additional symptomatic treatment as required.

Shivering after Pentothal for Injection anaesthesia, manifested by twitching face muscles and occasional progression to tremors of the arms, head, shoulders 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 anaesthesia employing nitrous oxide. Treatment consists of warming the patient with blankets and maintaining room temperature near 22°C (72°F).

**Preparation of solutions**
Pentothal for Injection is supplied as a yellowish, hygroscopic powder. Solutions should be prepared aseptically with one of the three following diluents:
Water for Injections BP, 
Sodium Chloride Injection BP 9 mg/mL (0.9%) or 
Glucose Injection BP 50 mg/mL (5%).
Clinical concentrations used for intermittent intravenous administration vary 
between 20 and 50 mg/mL. (See Table 2.) A 20 or 25 mg/mL solution is most 
commonly used. A 34 mg/mL concentration in water for injections is isotonic; 
concentrations less than 20 mg/mL in this diluent are not used because they 
cause haemolysis.
For continuous intravenous drip administration, concentrations of 2 or 4 mg/mL 
are used. Solutions may be prepared by adding Pentothal for Injection to 
Glucose Injection BP 50 mg/mL (5%), Sodium Chloride Injection BP 9 mg/mL 
(0.9%) or Normosol R pH 7.4. See Table 2.

Table 2
Pentothal for Injection Calculations for various concentrations

<table>
<thead>
<tr>
<th>Concentration desired (%)</th>
<th>Amounts to use (mg/mL)</th>
<th>Pentothal for Injection (g)</th>
<th>Diluent (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>2</td>
<td>1</td>
<td>500</td>
</tr>
<tr>
<td>0.4</td>
<td>4</td>
<td>1</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>500</td>
</tr>
<tr>
<td>2.0</td>
<td>20</td>
<td>5</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>500</td>
</tr>
<tr>
<td>2.5</td>
<td>25</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>5.0</td>
<td>50</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>

Since Pentothal for Injection contains no added bacteriostatic agent, extreme 
care in preparation and handling should be exercised at all times to prevent the 
introduction of microbial contaminants. Injection of air into the solution should be 
avoided because this may hasten the development of cloudiness. Solutions 
should be freshly prepared and used promptly and inspected visually for 
particulate matter and discolouration, whenever solution and container permit. To 
reduce microbiological hazard, use as soon as possible after reconstitution. If 
storage is necessary, hold at 2-8°C, for not more than 24 hours. Sterilisation by 
heating should not be attempted.

Compatibility
Any solutions of Pentothal for Injection with a visible precipitate should not be administered. The stability of Pentothal for Injection 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 Pentothal for Injection solutions will increase the likelihood of precipitation of thiopental acid. Such factors include the use of diluents that are too acid 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 Pentothal for Injection solutions. The most stable solutions are those 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 Pentothal for Injection.

OVERDOSAGE
Symptoms. Overdosage may occur from too rapid or repeated injections. Too rapid injection may be followed by an alarming fall in blood pressure even to shock levels. Apnea, occasional laryngospasm, coughing and other respiratory difficulties with excessive or too rapid injections may occur.

Treatment. 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. The lethal dose of barbiturates varies and cannot be stated with certainty. Lethal blood levels may be as low as 1 mg/100 mL for short acting barbiturates, less if other depressant drugs or alcohol are also present. Cardiovascular collapse may also occur and treatment should be directed toward supporting the blood pressure and using volume expansion and/or vasopressor agents, as appropriate.

In case of overdose, immediately contact 13 11 26, the Poisons Information Centre for advice.

PRESENTATION AND STORAGE CONDITIONS
Pentothal for Injection, 500 mg/20 mL, powder for Injection
Vials, 500 mg: pack of 25 and 50.
Store below 30°C AUST R 73505

NAME AND ADDRESS OF SPONSOR
Link Medical Products Pty Ltd.
5 Apollo Street
Warriewood
NSW 2102

POISON SCHEDULE OF THE MEDICINE
S4

DATE OF TGA APPROVAL:
29 April 2010

DATE OF MOST RECENT AMENDMENT
04 September 2013