



Additional Enclosures

1. PENTOTHAL® THIOPENTAL SODIUM FOR INJECTION, USP, Package Insert, October 2004.

2. pentothal 6431

PENTOTHAL®

THIOPENTAL SODIUM FOR INJECTION, USP



**WARNING: MAY BE
HABIT FORMING.**

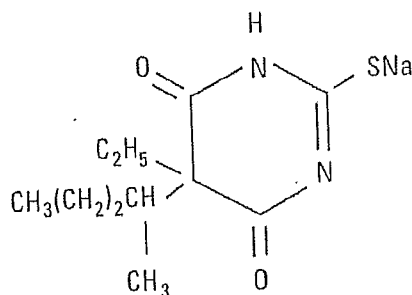
Rx Only

DESCRIPTION

Pentothal (Thiopental Sodium for Injection, USP) is a thiobarbiturate, the sulfur analogue of sodium pentobarbital.

The drug is prepared as a sterile powder and after reconstitution with an appropriate diluent is administered by the intravenous route.

Pentothal is chemically designated sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate and has the following structural formula:



The drug is a yellowish, hygroscopic powder, stabilized with anhydrous sodium carbonate as a buffer (60 mg/g of thiopental sodium).

CLINICAL PHARMACOLOGY

Pentothal (Thiopental Sodium for Injection, USP) is an ultrashort-acting depressant of the central nervous system which induces hypnosis and anesthesia, but not analgesia. It produces hypnosis within 30 to 40 seconds of intravenous injection. Recovery after a small dose is rapid, with some somnolence and retrograde amnesia. Repeated intravenous doses lead to prolonged anesthesia because fatty tissues act as a reservoir; they accumulate Pentothal in concentrations 6 to 12 times greater than the plasma concentration, and then release the drug slowly to cause prolonged anesthesia.

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

The distribution and fate of Pentothal (as with other barbiturates) is influenced chiefly by its lipid solubility (partition coefficient), protein binding and extent of ionization. Pentothal has a partition coefficient of 580.

Approximately 80% of the drug in the blood is bound to plasma protein. Pentothal is largely degraded in the liver and to a smaller extent in other tissues, especially the kidney and brain. It has a pK_a of 7.4.

Concentration in spinal fluid is slightly less than in the plasma.

Biotransformation products of thiopental are pharmacologically inactive and mostly excreted in the urine.

INDICATIONS AND USAGE

Pentothal (Thiopental Sodium for Injection, USP) is indicated (1) as the sole anesthetic agent for brief (15 minute) procedures, (2) for induction of anesthesia prior to administration of other anesthetic agents, (3) to supplement regional anesthesia, (4) to provide hypnosis during balanced anesthesia with other agents for analgesia or muscle relaxation, (5) for the control of convulsive states during or following inhalation anesthesia, local anesthesia, or other causes, (6) in neurosurgical patients with increased intracranial pressure, if adequate ventilation is provided, and (7) for narcoanalysis and narcosynthesis in psychiatric disorders.

CONTRAINDICATIONS

Absolute Contraindications:

(1) Absence of suitable veins for intravenous administration, (2) hypersensitivity (allergy) to barbiturates and (3) variegate porphyria (South African) or acute intermittent porphyria.

Relative Contraindications:

(1) Severe cardiovascular disease, (2) hypotension or shock, (3) 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, and (4) status asthmaticus.

WARNINGS

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.

Avoid extravasation or intra-arterial injection.

WARNING: MAY BE HABIT FORMING.

PRECAUTIONS

Observe aseptic precautions at all times in preparation and handling of Pentothal (Thiopental Sodium for Injection, USP) solutions.

If used in conditions involving relative contraindications, reduce dosage and administer slowly.

Care should be taken in administering the drug to patients with advanced cardiac disease, increased intracranial pressure, ophthalmoplegia plus, asthma, myasthenia gravis and endocrine insufficiency (pituitary, thyroid, adrenal, pancreas).

Drug interactions: The following drug interactions have been reported with thiopental.

Drug	Effect
Probenecid	Prolonged action of thiopental
Diazoxide	Hypotension
Zimelidine	Thiopental antagonism
Opioid analgesics	Decreased antinociceptive action
Aminophylline	Thiopental antagonism
Midazolam	Synergism

Nursing Mothers: Thiopental sodium readily crosses the placental barrier and small amounts may appear in the milk of nursing mothers following administration of large doses.

Pregnancy Category C. Animal reproduction studies have not been conducted with Pentothal. It is also not known whether Pentothal can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pentothal should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Adverse reactions include respiratory depression, myocardial depression, cardiac arrhythmias, prolonged somnolence and recovery, sneezing, coughing, bronchospasm, laryngospasm and shivering. Anaphylactic and anaphylactoid reactions to Pentothal (Thiopental Sodium for Injection, USP) have been reported. Symptoms, e.g., urticaria, bronchospasm, vasodilation and edema should be managed by conventional means.

Rarely, immune hemolytic anemia with renal failure and radial nerve palsy have been reported.

DRUG ABUSE AND DEPENDENCE

WARNING: MAY BE HABIT FORMING.

Thiopental sodium is classified as a Schedule III controlled substance.

OVERDOSAGE

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. 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.

MANAGEMENT OF OVERDOSAGE

It is generally agreed that respiratory depression or arrest due to unusual sensitivity to thiopental sodium or overdosage is easily managed if there is no concomitant respiratory obstruction. If the airway is patent, any method of ventilating the lungs (that prevents hypoxia) should be successful in maintaining other vital functions. Since depression of respiratory activity is one of the characteristic actions of the drug, it is important to observe respiration closely.

Should laryngeal spasm occur, it may be relieved by one of the usual methods, such as the use of a relaxant drug or positive pressure oxygen. Endotracheal intubation may be indicated in difficult cases.

DOSAGE AND ADMINISTRATION

Pentothal 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 middle-aged 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. Sodium pentobarbital injection (Nembutal®) is suggested because it provides a preliminary indication of how the patient will react to barbiturate anesthesia. 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 25 to 75 mg (1 to 3 mL of a 2.5% solution) of Pentothal (Thiopental Sodium for Injection, USP) to assess tolerance or unusual sensitivity to Pentothal, 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 Pentothal, (2) the solution may be more concentrated than had been assumed, or (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 (2 to 3 mL of a 2.5% solution) 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 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. Blood pressure usually falls slightly but returns toward 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 Pentothal (Thiopental Sodium for Injection, USP) is used for induction in balanced anesthesia with a skeletal muscle relaxant and an inhalation agent, the total dose of Pentothal 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. As an initial dose, 210 to 280 mg (3 to 4 mg/kg) of Pentothal is usually required for rapid induction in the average adult (70 kg).

When Pentothal (Thiopental Sodium for Injection, USP) 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.

Use in Convulsive States

For the control of convulsive states following anesthesia (inhalation or local) or other causes, 75 to 125 mg (3 to 5 mL of a 2.5% solution) should be given as soon as possible after the convulsion begins. Convulsions following the use of a local anesthetic may require 125 to 250 mg of Pentothal given over a ten minute period. If the convulsion is caused by a local anesthetic, the required dose of Pentothal will depend upon the amount of local anesthetic 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 of body weight may be given to reduce intraoperative elevations of intracranial pressure, if adequate ventilation is provided.

Use in Psychiatric Disorders

For narcoanalysis and narcosynthesis in psychiatric disorders, premedication with an anticholinergic agent may precede administration of Pentothal. After a test dose, Pentothal (Thiopental Sodium for Injection, USP) is injected at a slow rate of 100 mg/min (4 mL/min of a 2.5% solution) 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, Pentothal 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.

MANAGEMENT OF SOME COMPLICATIONS

Respiratory depression (hypoventilation, apnea), which may result from either unusual responsiveness to Pentothal or overdosage, is managed as stated above. Pentothal 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 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. 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 (Thiopental Sodium for Injection, USP) does not sensitize the heart to epinephrine or other sympathomimetic amines.

Extravascular infiltration should be avoided. Care should be taken to insure that the needle is within the lumen of the vein before injection of Pentothal. 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 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 Pentothal (Thiopental Sodium for Injection, USP) 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 after Pentothal 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 (72° F), and administration of chlorpromazine or methylphenidate.

PREPARATION OF SOLUTIONS

Pentothal (Thiopental Sodium for Injection, USP) is supplied as a yellowish, hygroscopic powder in a variety of different containers. Solutions should be prepared aseptically with one of the three following diluents: Sterile Water for Injection, USP, 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. 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 Pentothal to 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP or Normosol®-R pH 7.4.

Since Pentothal 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.

WARNING: The 2.5 g and larger sizes contain adequate medication for several patients.

COMPATIBILITY

Any solution of Pentothal (Thiopental Sodium for Injection, USP) with a visible precipitate should not be administered. The stability of Pentothal 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 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 succinylcholine, tubocurarine or other drugs which have an acid pH should not be mixed with Pentothal solutions. The most stable solutions are those reconstituted in water or isotonic saline, 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.

CALCULATIONS FOR VARIOUS CONCENTRATIONS

Concentration Desired		Amounts to Use	
Percent	mg/mL	Pentothal g	Diluent mL
0.2	2	1	500
0.4	4	1	250
		{ 2	500
2.0	20	5	250
		{ 10	500
2.5	25	1	40
		{ 5	200
5	50	1	20
		{ 5	100

Reconstituted solutions of Pentothal (Thiopental Sodium for Injection, USP) should be inspected visually for particulate matter and discoloration, whenever solution and container permit.

HOW SUPPLIED

Pentothal is available in a variety of sizes and containers shown at the end of this insert.

Diluents in Pentothal® Kits

READY-TO-MIX SYRINGES AND VIALS

(For preparing solutions of Thiopental Sodium for Injection, USP)

DESCRIPTION

The following diluents in various container, syringe and vial sizes are provided in Pentothal Kits, Pentothal Ready-to-Mix Syringes and Vials for preparing solutions of Pentothal (Thiopental Sodium for Injection, USP) for clinical use:

Sterile Water for Injection, USP is a sterile, nonpyrogenic preparation of water for injection which contains no bacteriostat, antimicrobial agents or added buffers. The pH is 5.7 (5.0 to 7.0).

Sterile Water for Injection, USP is a pharmaceutic aid (solvent) for intravenous administration only after addition of a solute.

Water is chemically designated H₂O.

0.9% Sodium Chloride Injection, USP is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection. Each mL contains sodium chloride 9 mg (308 mOsmol/liter calc). It contains no bacteriostat, antimicrobial agents or added buffers except for pH adjustment. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. pH is 5.7 (4.5 to 7.0).

0.9% Sodium Chloride Injection, USP is an isotonic vehicle for intravenous administration of another solute.

Sodium chloride is chemically designated NaCl, a white crystalline compound freely soluble in water.

The semi-rigid vial contained in List Nos. 3329 and 6435 is fabricated from a specially formulated polyolefin. It is a copolymer of ethylene and propylene. The safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers. The container requires no vapor barrier to maintain the proper labeled volume.

CLINICAL PHARMACOLOGY

Sterile Water for Injection, USP serves only as a pharmaceutic aid for diluting or dissolving drugs prior to administration.

Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight. Average normal adult daily requirement ranges from two to three liters (1.0 to 1.5 liters each for insensible water loss by perspiration and urine excretion).

Water balance is maintained by various regulatory mechanisms. Water distribution depends primarily on the concentration of dissociated electrolytes in the body compartments and sodium (Na^+) plays a major role in maintaining a physiologic equilibrium between fluid intake and output.

0.9% Sodium Chloride Injection, USP serves only as an isotonic vehicle for drugs prior to administration.

Sodium chloride in water is an electrolyte solution of sodium (Na^+) and chloride (Cl^-) ions. These ions are normal constituents of the body fluids (principally extracellular) and are essential for maintaining electrolyte balance.

The distribution and excretion of sodium (Na^+) and chloride (Cl^-) are largely under the control of the kidney which maintains a balance between intake and output of these ions.

The small volumes of fluid and amounts of sodium chloride provided by 0.9% Sodium Chloride Injection in Ready-to-Mix Syringes are unlikely to produce a significant effect on fluid or electrolyte balance.

INDICATIONS AND USAGE

These products are indicated only for preparing Pentothal (Thiopental Sodium for Injection, USP) solutions for clinical use.

CONTRAINDICATIONS

Do not use unless the diluent is clear and the bottle or vial seal or syringe package is undamaged.

Diluents in Pentothal Kits, Ready-to-Mix Syringes or Vials should not be used for fluid or sodium chloride replacement.

WARNINGS

Intravenous administration of Sterile Water for Injection, USP without a solute may result in hemolysis.

Use aseptic technique for preparing Pentothal solutions when using Pentothal Kits, Syringes or Vials and during withdrawal from reconstituted single or multiple-use containers.

Administer only clear reconstituted solutions.

Use within 24 hours after reconstitution. Discard unused portions.

PRECAUTIONS

Do not use unless solution is clear and container is undamaged.

Inspect reconstituted (mixed) solutions of Pentothal (Thiopental Sodium for Injection, USP) for clarity and freedom from precipitation or discoloration prior to administration. Use reconstituted solution only if it is clear, free from precipitate and not discolored.

Use Transfer Label in each Pentothal Kit and affix to container of reconstituted solution to show concentration and time of preparation.

Pregnancy Category C. Animal reproduction studies have not been conducted with sterile water for injection or sodium chloride injection. It is also not known whether sterile water or sodium chloride injection containing additives can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sterile water for injection or sodium chloride injection with additives should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Reactions which may occur because of the diluents, technique of preparation or mixing, or administration of reconstituted solutions of Pentothal include febrile response or infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection and extravasation.

If an adverse reaction does occur, discontinue the injection, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of unused solution (or the used container or syringe) for examination if deemed necessary.

DRUG ABUSE AND DEPENDENCE

None known.

OVERDOSAGE

Used as diluents for preparing solutions of Pentothal (Thiopental Sodium for Injection, USP) the small volumes of administered fluid (from Sterile Water for Injection in bottles and vials) and amounts of sodium chloride (from 0.9% Sodium Chloride Injection in Ready-to-Mix Syringes) are unlikely to pose a threat of fluid or sodium chloride overload.

DOSAGE AND ADMINISTRATION

Pentothal solutions should be administered only by intravenous injection and by individuals experienced in the conduct of intravenous anesthesia.

The volume and choice of diluent for preparing Pentothal (Thiopental Sodium for Injection, USP) solutions for clinical use depends on the concentration and vehicle desired. Pentothal Kits provide only Sterile Water for Injection as the diluent for individual or multi-patient use; Pentothal Ready-to-Mix Syringes provide only 0.9% Sodium Chloride Injection, USP as the diluent for individual patient use; vials provide only Sterile Water for Injection, USP as the diluent for individual patient use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See PRECAUTIONS.

HOW SUPPLIED

The diluent in Pentothal Kits is supplied in various size containers with various dosage sizes of Pentothal (Thiopental Sodium for Injection, USP). Kits include all items needed for aseptic transfer of Pentothal powder from a squeeze bottle into the diluent container.

The diluent in Pentothal Ready-to-Mix Syringes is supplied in a separate container to permit mixing with the Pentothal in a powder vial to permit immediate intravenous injection of reconstituted solution into a vein or attachment to a standard stopcock assembly.

Vials are supplied in cartons with different dosage sizes of Pentothal for preparing 2.0% or 2.5% concentrations by using a separate syringe (not supplied) for mixing.

See table for list of sizes available.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Keep reconstituted solution in a cool place.

Table: Pentothal® (Thiopental Sodium for Injection, USP) and Diluent in Kits, Ready-to-Mix Syringes and Ready-to-Mix LifeShield® Syringes

List No.	Pentothal	Pentothal Container	Diluent (mL)*	Diluent Container	Theoretical Reconstituted Conc.
6108 (Kit)	5 g	Squeeze Bottle	W (250)	PF Bottle	2% (20 mg/mL)
6244 (Kit)	1 g	Squeeze Bottle	W (40)	PF Bottle	2.5% (25 mg/mL)
6435 (Kit)	1 g	Vial	W (50)	Plastic Vial	2% (20 mg/mL)
3329 (Kit)	500 mg	Vial	W (20)	Plastic Vial	2.5% (25 mg/mL)
9087 (Kit)	1 g	Vial	W (50)	Plastic Vial	2% (20 mg/mL)
6246 (Ready-to-Mix Syringe)	400 mg	Syringe	S (20)	Syringe	2% (20 mg/mL)
6241 (Ready-to-Mix Syringe)	250 mg	Syringe	S (10)	Syringe	2.5% (25 mg/mL)
6243 (Ready-to-Mix Syringe)	500 mg	Syringe	S (20)	Syringe	2.5% (25 mg/mL)
3351 (Ready-to-Mix LifeShield Syringe)	250 mg	Syringe	S (10)	Plastic Vial	2.5% (25 mg/mL)
3352 (Ready-to-Mix LifeShield Syringe)	400 mg	Syringe	S (20)	Plastic Vial	2% (20 mg/mL)
3353 (Ready-to-Mix LifeShield Syringe)	500 mg	Syringe	S (20)	Plastic Vial	2.5% (25 mg/mL)

*Diluent containers are slightly overfilled to assure compliance with USP minimum fill volume requirements.

PF — denotes Partial-Fill

W — denotes Sterile Water for Injection, USP

S — denotes 0.9% Sodium Chloride Injection, USP

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Pentothal®



**THIOPENTAL SODIUM
FOR INJECTION, USP**

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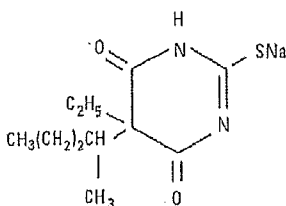
R_x only

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

The distribution and fate of Pentothal (as with other barbiturates) is influenced chiefly by its lipid solubility (partition coefficient), protein binding and extent of ionization. Pentothal has a partition coefficient of 580.

Approximately 80% of the drug in the blood is bound to plasma protein. Pentothal is largely degraded in the liver and to a smaller extent in other tissues, especially the kidney and brain. It has a pK_a of 7.4.

Concentration in spinal fluid is slightly less than in the plasma.

Biotransformation products of thiopental are pharmacologically inactive and mostly excreted in the urine.

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CONTRAINDICATIONS

Absolute Contraindications:

(1) Absence of suitable veins for intravenous administration, (2) hypersensitivity (allergy) to barbiturates and (3) variegate porphyria (South Africa) or acute intermittent porphyria.

Relative Contraindications:

(1) Severe cardiovascular disease, (2) hypotension or shock, (3) 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 and myasthenia gravis and (4) status asthmaticus.

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Avoid extravasation or intra-arterial injection.

WARNING: MAY BE HABIT FORMING.

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Drug Interactions: The following drug interactions have been reported with thiopental:

Drug	Effect
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Diazoxide	Hypotension
Zimelidine	Thiopental antagonism
Opioid analgesics	Decreased antinociceptive action
Aminophylline	Thiopental antagonism
Midazolam	Synergism

For Pediatric Use, refer to DOSAGE AND ADMINISTRATION.

Nursing Mothers: Thiopental sodium readily crosses the placental barrier and small amounts may appear in the milk of nursing mothers following administration of large doses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies of thiopental sodium in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy Category C. 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 reproduction capacity. Thiopental sodium should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Adverse reactions to thiopental sodium include respiratory depression, myocardial depression, cardiac arrhythmias, prolonged somnolence and recovery, sneezing, coughing, bronchospasm, laryngospasm and shivering. Anaphylactic and anaphylactoid reactions to Pentothal (Thiopental Sodium for Injection, USP) have been reported. Symptoms, e.g., urticaria, bronchospasm, vasodilation and edema should be managed by conventional means.

Rarely, immune hemolytic anemia with renal failure and radial nerve palsy have been reported.

DRUG ABUSE AND DEPENDENCE

Thiopental sodium is classified as a Schedule III controlled substance.

OVERDOSAGE

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. 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.

MANAGEMENT OF OVERDOSAGE

It is generally agreed that respiratory depression or arrest due to unusual sensitivity to thiopental sodium or overdosage is easily managed if there is no concomitant respiratory obstruction. If the airway is patent, any method of ventilating the lungs (that prevents hypoxia) should be successful in maintaining other vital functions. Since depression of respiratory activity is one of the characteristic actions of the drug, it is important to observe respiration closely.

Should laryngeal spasm occur, it may be relieved by one of the usual methods, such as the use of a relaxant drug or positive pressure oxygen. Endotracheal intubation may be indicated in difficult cases.

MANAGEMENT OF SOME COMPLICATIONS

Respiratory depression (hypoventilation, apnea), which may result from either unusual responsiveness to Pentothal (Thiopental Sodium for Injection, USP) or overdosage, is managed as stated above. Pentothal 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 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. 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 PCO_2 is elevated, but they are uncommon with adequate ventilation. Management of myocardial depression is the same as for overdosage. Pentothal (Thiopental Sodium for Injection, USP) does not sensitize the heart to epinephrine or other sympathomimetic amines.

Extravascular infiltration should be avoided. Care should be taken to insure that the needle is within the lumen of the vein before injection of Pentothal. 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 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 Pentothal (Thiopental Sodium for Injection, USP) 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 after Pentothal 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 (72° F), and administration of chlorpromazine or methylphenidate.

DOSAGE AND ADMINISTRATION

Pentothal (Thiopental Sodium for Injection, USP) should be administered by the intravenous route only by individuals experienced in the administration of intravenous anesthesia. 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 middle-aged 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. Sodium pentobarbital injection (Nembutal®) is suggested because it provides a preliminary indication of how the patient will react to barbiturate anesthesia. 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 25 to 75 mg (1 to 3 mL of a 2.5% solution) of Pentothal (Thiopental Sodium for Injection, USP) to assess tolerance or unusual sensitivity to Pentothal, 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 Pentothal, (2) the solution may be more concentrated than had been assumed, or (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 (2 to 3 mL of a 2.5% solution) 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 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. Blood pressure usually falls slightly but returns toward 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 Pentothal (Thiopental Sodium for Injection, USP) is used for induction in balanced anesthesia with a skeletal muscle relaxant and an inhalation agent, the total dose of Pentothal 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. As an initial dose, 210 to 280 mg (3 to 4 mg/kg) of Pentothal is usually required for rapid induction in the average adult (70 kg).

When Pentothal (Thiopental Sodium for Injection, USP) 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.

Use in Convulsive States

For the control of convulsive states following anesthesia (inhalation or local) or other causes, 75 to 125 mg (3 to 5 mL of a 2.5% solution) should be given as soon as possible after the convulsion begins. Convulsions following the use of a local anesthetic may require 125 to 250 mg of Pentothal (Thiopental Sodium for Injection) given over a ten minute period. If the convulsion is caused by a local anesthetic, the required dose of Pentothal will depend upon the amount of local anesthetic 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 of body weight may be given to reduce intraoperative elevations of intracranial pressure, if adequate ventilation is provided.

Use in Psychiatric Disorders

For narcoanalysis and narcosynthesis in psychiatric disorders, premedication with an anticholinergic agent may precede administration of Pentothal. After a test dose, Pentothal is injected at a slow rate of 100 mg/min (4 mL/min of a 2.5% solution) 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, Pentothal (Thiopental Sodium for Injection, USP) 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.

Preparation of Solutions

Pentothal (Thiopental Sodium for Injection, USP) should be prepared aseptically with one of the three following diluents: Sterile Water for Injection, USP, 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. 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 Pentothal to 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP or Normosol®-R pH 7.4.

Since Pentothal 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.

Calculations for Various Concentrations

Concentration Desired	Percent mg/mL	Amounts to Use	
		Pentothal g	Diluent mL
0.2	2	1	500
0.4	4	1	250
2.0	20	1	50
2.5	25	{ 5	250
		{ 1	40
5	50	{ 5	200
		{ 1	20
		{ 5	100

Reconstituted solutions of Pentothal (Thiopental Sodium for Injection, USP) should be inspected visually for particulate matter and discoloration, whenever solution and container permit.

Compatibility

Any solution of Pentothal (Thiopental Sodium for Injection, USP) with a visible precipitate should not be administered. The stability of Pentothal 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 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 succinylcholine, tubocurarine or other drugs which have an acid pH should not be mixed with Pentothal solutions. The most stable solutions are those reconstituted in water or isotonic saline, 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.

HOW SUPPLIED

Pentothal (Thiopental Sodium for Injection, USP) is available in the following sizes and containers.

List No.	Grams	Container
6431-02	1 gram	50 mL container
6431-03	5 gram	250 mL container

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Keep reconstituted solution in a cool place.

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