SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

THIOSOL

Thiopental sodium for Injection BP

Strength:

500 mg / vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Sr. No.	Particulars	Grade	Qty. / vial	Function
1.	Sterile Thiopental Sodium	BP	500 mg	Active

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:

Powder for Injection

Yellowish white crystalline hygroscopic powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

1. Thiopental sodium is used for the induction of general anaesthesia and is also used as an adjunct to provide hypnosis during balanced anaesthesia with other anaesthetic agents, including analgesics and muscle relaxants.
2. Thiopental sodium is also used as an adjunct for control of convulsive disorders of various aetiology, including those caused by local anaesthetics.
3. Thiopental sodium has now been used to reduce the intracranial pressure in patients with increased intracranial pressure, if controlled ventilation is provided.

4.2 Posology and method of administration:

Route of Administration: For Intravenous Injection

Intravenous injection:

Thiopental sodium 500mg/1g injection is administered intravenously normally as a 2.5%w/v (500mg in 20ml)/(1g in 40ml) solution. On occasions it may be administered as a 5%w/v solution (500mg in 10ml)/(1g in 20ml). The intravenous injection preparation should be used after reconstitution of the sterile powder with Water for Injections, usually to produce a 2.5% w/v solution and this should be discarded after seven hours.

Use in anaesthesia:

Normal dosage for the induction of anaesthesia is 100mg to 150mg injected over 10 to 15 seconds. If necessary a repeat dose of 100mg to 150mg may be given after one minute. No fixed dosage recommendations for the intravenous injection can be given, since the dosage will need to be carefully adjusted according to the patient's response. Factors such as age, sex, and weight of the patient should be taken into consideration. Thiopental sodium reaches effective concentrations in the brain within 30 seconds and anaesthesia is normally produced within one minute of an intravenous dose.

Adult:

100mg to 150mg intravenously over 10 seconds to 15 seconds, normally as a

2.5% w/v solution. A repeat dose of 100mg to 150mg may be given after one minute. The intravenous injection should be given slowly and the amounts given titrated against the patient's response to minimize the risk of respiratory depression or the possibility of overdosage. The average dose for an adult of 70kg is roughly 200mg to 300mg (8ml to 12ml of a 2.5% w/v solution) with maximum of 500mg and 400mg to 600mg (16ml to 24ml of a 2.5% w/v solution) with maximum of 1g.

Children:
2 to 7mg/kg bodyweight, intravenously over 10 to 15 seconds, normally as a 2.5% w/v solution. A repeat dose of 2 to 7mg/kg may be given after one minute. The dose is 2 to 7mg/kg based on the patient's response. The dose for children should not exceed 7mg/kg.

Elderly:
Smaller adult doses are advisable.

Use in convulsive states:
75mg to 125mg (3ml to 5ml of a 2.5% w/v solution) should be given as soon as possible after the convulsion begins. Further doses may be required to control convulsions following the use of a local anaesthetic. Other regimens, such as the use of intravenous or rectal diazepam, may be used to control convulsive states.

Use in neurological patients with raised intracranial pressure:
Intermittent bolus injections of 1.5 to 3mg/kg of body weight may be given to reduce elevations of intracranial pressure if controlled ventilation is provided.

RECONSTITUTION OF SOLUTION
Thiosol (Thiopental Sodium for Injection B.P.) solutions should be prepared aseptically with the following diluents: Sterile Water for Injection USP. Reconstitute 500mg Thiosol with 20mL Sterile Water for Injection USP. Reconstitute 1g Thiosol with 20mL Sterile Water for Injection USP. Clinical concentrations used for intermittent intravenous administration vary between 2.0% w/v and 5.0% w/v. A 2.0% w/v or 2.5% w/v solution is most commonly used. A 3.4% w/v concentration in sterile water for injection is isotonic; concentrations less than 2.0% w/v in this diluent are not used because they cause hemolysis. For continuous intravenous drip administration, concentrations of 0.2% w/v or 0.4% w/v are used. Solutions may be prepared by adding Thiosol to 5% w/v Dextrose Injection USP, 0.9% w/v Sodium Chloride Injection USP.
Since Thiosol 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 immediately after preparation. Sterilization by heating should not be attempted.

4.3 Contraindications:

Thiopental sodium is contra-indicated in respiratory obstruction, acute asthma, severe shock and dystrophia myotonica. Administration of any barbiturate is contra-indicated

in porphyria. Care should also be exercised with severe cardiovascular diseases, severe respiratory diseases and hypertension of various aetiology. Patients with hypersensitivity reactions to barbiturates.

4.4 Special warnings and precautions for use:

Thiopental sodium causes respiratory depression and a reduction in cardiac output and may precipitate acute circulatory failure in patients with cardiovascular disease, particularly constrictive pericarditis.

When particular caution is required :
Special care is needed in administering thiopental sodium to patients with the following conditions:- hypovolaemia, severe haemorrhage, burns, cardiovascular disease, status asthmaticus, myasthenia gravis, adrenocortical insufficiency (even when controlled by cortisone), cachexia, raised intracranial pressure and raised blood urea.

Dose reduction required :
Reduced doses are recommended in shock, dehydration, severe anaemia, hyperkalaemia, toxaemia, metabolic disorders e.g. thyrotoxicosis, myxoedema and diabetes.

Use in hepatic and renal disease :
Thiopental sodium is metabolised primarily by the liver so doses should be reduced in patients with hepatic impairment. Barbiturate anaesthetics should be used with caution in severe renal disease. Reduced doses are also indicated in the elderly and in patients who have been premedicated with narcotic analgesics.

Use with other medications and in underlying disease :
Thiopental sodium has been shown to interact with sulphafurazole. Reduced initial doses may be required to achieve adequate anaesthesia, but repeat doses may also be necessary to maintain anaesthesia. Patients taking longterm medications such as aspirin, oral anticoagulants, oestrogens, MAOIs and lithium may need to adjust the dose or stop therapy prior to elective surgery. Patients with diabetes or hypertension may need to adjust their therapy before anaesthesia.

Increased doses:
Increased doses may be necessary in patients who have either a habituation or addiction to alcohol or drugs of abuse. Under these circumstances it is recommended that supplementary analgesic agents are used.

Extravasation :
Extravasation causes local tissue necrosis and severe pain. This can be relieved by application of an ice pack and local injection of hydrocortisone. The 5% w/v solution is hypertonic and may cause pain on injection and thrombophlebitis.

Accidental intra-arterial injection :
Accidental intra-arterial injection of thiopental sodium causes severe arterial spasm and an intense burning pain around the injection site. In the case of accidental intra-arterial injection of thiopental the needle should be left insitu

so that an injection of an antispasmodic, such as papaverine or prilocaine hydrochloride may be given. Anticoagulant therapy may also be started to reduce the risk of thrombosis.

Use during pregnancy and lactation :
Thiopental sodium readily crosses the placental barrier and also appears in breast milk. Therefore, breast-feeding should be temporarily suspended or breast milk expressed before the induction of anaesthesia. It has been shown that thiopental sodium can be used without adverse effects during pregnancy although the total dose should not exceed 250mg. However, when considering use of thiopental sodium the clinician should only use the drug when the expected benefits outweigh any potential risks.

Effects on ability to drive and use machines :
Post-operative vertigo, disorientation and sedation may be prolonged and out-patients given thiopental sodium should therefore be advised not to drive or use machinery, especially within the first 24 to 36 hours.

4.5 Interaction with other medicinal products and other forms of interaction:
Thiopental sodium has been shown to interact with sulphafurazole. It should be noted that thiopental will interact with beta-blockers and calcium antagonists causing a fall in blood pressure.

ACE inhibitors : enhanced hypotensive effect when general anaesthetics given with ACE inhibitors.

Adrenergic neurone blockers: Enhanced hypotensive effect when general anaesthetics given with adrenergic neurone blockers.

Alpha-blockers : Enhanced hypotensive effect when general anaesthetics given with alpha-blockers.

Analgesics: Pretreatment with aspirin has been shown to potentiate thiopental sodium anaesthesia. Opioid analgesics can potentiate the respiratory depressant effect of barbiturate anaesthetics and the dose of anaesthetic may need to be reduced. The analgesic effect of pethidine can be reduced by thiopental sodium.

Angiotensin-II receptor antagonists: Enhanced hypotensive effect when general anaesthetics given with angiotensin-II receptor antagonists.

Antibacterials: General anaesthetics possibly potentiate hepatotoxicity of isoniazid; effects of thiopental sodium enhanced by sulphonamides; hypersensitivity-like reactions can occur when general anaesthetics given with intravenous vancomycin.

Antidepressants: Increased risk of arrhythmias and hypotension when general anaesthetics given with tricyclic antidepressants. Hypotension and hypertension has been seen with MAOIs.

Antipsychotics: Patients being treated with phenothiazine antipsychotics may experience increased hypotension. Some phenothiazines, especially promethazine, may also increase the incidence of excitatory phenomena produced by barbiturate

anaesthetics; cyclizine may possibly have a similar effect. The sedative properties may be also potentiated by thiopental sodium.

Benzodiazepines: Midazolam potentiates the anaesthetic effects of thiopental sodium.

Diazoxide: Enhanced hypotensive effect when general anaesthetics given with diazoxide.

Diuretics: Enhanced hypotensive effect when general anaesthetics given with diuretics.

Gastrointestinal drugs: Metoclopramide and droperidol reduce the dose of thiopental sodium required to induce anaesthesia.

Methyldopa: enhanced hypotensive effect when general anaesthetics given with methyldopa.

Moxonidine: Enhanced hypotensive effect when general anaesthetics given with moxonidine

Nitrates: Enhanced hypotensive effect when general anaesthetics given with nitrates.

Probenecid: Pretreatment with probenecid has been shown to potentiate thiopental sodium anaesthesia.

Vasodilator antihypertensives: Enhanced hypotensive effect when general anaesthetics given with hydralazine, minoxidil or nitroprusside.
The use of anaesthetics with other CNS depressant drugs such as those used for premedication may produce synergistic effects on the CNS and, in some cases; a smaller dose of general anaesthetic should be used. Bradycardia occurring during anaesthetic induction with thiopental has been reported in patients also receiving fentanyl.

4.6 Fertility, pregnancy and lactation:

Thiopental sodium readily crosses the placental barrier and also appears in breast milk. Therefore, breast-feeding should be temporarily suspended or breast milk expressed before the induction of anaesthesia. It has been shown that thiopental sodium can be used without adverse effects during pregnancy although the total dose should not exceed 250mg. However, when considering use of thiopental sodium the clinician should only use the drug when the expected benefits outweigh any potential risks.

4.7 Effects on ability to drive and use machines:

Post-operative vertigo, disorientation and sedation may be prolonged and out-patients given thiopental sodium should therefore be advised not to drive or use machinery, especially within the first 24 to 36 hours.

4.8 Undesirable effects:

ADVERSE REACTIONS
Laryngeal spasm may occur, together with coughing or sneezing, during the

induction procedure. For this reason it is not advised to use thiopental sodium alone for peroral endoscopy. Excessive doses are associated with hypothermia and profound cerebral impairment. An initial fall in blood pressure is often seen. Postoperative vomiting is infrequent, but shivering may occur and there may be persistent drowsiness, confusion and amnesia.
Other relatively common postoperative effects include anorexia, malaise, fatigue, and dizziness. Delirium has been noted in elderly patients. Allergic reactions, skin reactions and hypersensitivity have been rarely reported. Bronchospasm, respiratory depression and myocardial depression or cardiac arrhythmias may occur. Headache is also reported with the use of barbiturate anaesthetics.

4.9 Overdose:

Overdosage produces acute respiratory depression, hypotension, circulatory failure and apnoea. Treatment must be artificial ventilation, lowering of the patient's head and infusion of plasma volume expanders.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Thiopental sodium is a short-acting substituted barbiturate that is more lipid soluble than other groups of barbiturates. The drug reversibly depresses the activity of all excitable tissues. The CNS is particularly sensitive and normally a general anaesthesia can be achieved with thiopental sodium without significant effects on peripheral tissues. Thiopental sodium acts through the CNS with particular activity in the mesencephalic reticular activating system. The barbiturates exert different effects on synaptic transmission, mostly those dependent on GABA. Autonomic ganglia of the peripheral nervous system are also depressed.

5.2 Pharmacokinetic properties:

Following intravenous administration, unconsciousness occurs within 30 seconds and will be continued for 20 to 30 minutes after a single dose. Rapid uptake occurs to most vascular areas of the brain followed by redistribution into other tissues. Thiopental sodium is strongly bound to plasma protein, which impairs excretion through the kidney. The metabolites are usually inactive and are then excreted. Thiopental sodium, therefore, whilst having a short duration of action, may have a long elimination phase.

5.3 Pre-clinical Safety Data:

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

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

None

6.2 Incompatibilities:

Any solution of Thiopental powder for solution for injection, with a visible precipitate should not be administered.

The stability of Thiopental powder for solution 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 orcondition which tends to lower pH (increase acidity) of Thiopental powder for solution for injection solutions will increasethe likelihood of precipitation of thiopental acid. Such factors include the use of diluents which are too acidic and theabsorption 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 Thiopentalpowder for solution for injection solutions. The most stable solutions are those reconstituted in water and/or isotonic saline and/or solution of dextrose, kept underrefrigeration and tightly stoppered.
The presence or absence of a visible precipitate offers a practical guide to the physical compatibility of preparedsolutions of Thiopental powder for solution for injection.

6.3 Shelf – life:
24 Months

6.4 Special precautions for storage:
Store below 30°C., protected from light.

6.5 Nature and contents of container:
Primary Container : 20 ml Flint USP-I tubular vial Stoppered with 20 mm GBBRS & Seal. with 20 mm purple “NEON” Embo. Lacquered Aluminium seal.

Presentation (Pack Size) : 20 ml Flint USP-I tubular vial stoppered with 20 mm GBBRS & Seal with 20mm purple “NEON” Embo. Lacquered Aluminium seal.

6.6 Special Precautions for Handling and Disposal:
Preparation of solutions
Thiopental powder for solution for injection is supplied as a yellowish, hygroscopic powder in a vial.
Solutions should beprepared aseptically with one of the three following diluents:
- water for injection (according Ph.Eur.),
- 0.9% sodium chloride solution for infusion (9 mg/ml),
- 5% dextrose solution for infusion (50 mg/ml).

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 injections 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

Desired concentration		**Amounts to use**	
%	mg/ml	g of Thiopental	ml of diluent
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
5.0	50	1	20
		5	100

Since Thiopental Injection contains no added bacteriostatic agent, extreme care in preparation and handling should beexercised 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 vapour should not be attempted.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER:

M/s. NEON LABORATORIES LIMITED
140, Damji Shamji Industrial Complex,
28, Mahal Indl. Estate, Mahakali Caves Road,
Andheri (East), Mumbai - 400 093

8. MARKETING AUTHORIZATION NUMBER:

07297/09072/NMR/2021

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORISATION:

29 April 2022

10. DATE OF REVISION OF THE TEXT:

July 2023

11. REFERENCE

Thiopental powder for solution for injection - Summary of Product Characteristics (SmPC) - print friendly - (emc)
(https://www.medicines.org.uk/emc/product/665/smpc/print)