Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Thiopental Sodium 500 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg thiopental sodium (as thiopental sodium and sodium carbonate).
Contains 53.5mg sodium per vial

For full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection (Powder for Injection)

Yellow-white freeze dried powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Thiopental sodium is given intravenously to induce short duration general anaesthesia. It is also indicated as an induction agent, and for the control of convulsive disorders. It may be used rectally to produce basal anaesthesia.
Thiopental sodium may be used to reduce the intracranial pressure in patients with increased intracranial pressure, if controlled ventilation is provided.

4.2 Posology and method of administration

Posology

Thiopental sodium is administered normally as a 2.5% w/v (500mg in 20ml) solution. On occasions it may be administered as a 5% solution (500mg in 10ml).

A test dose of 25mg to 75mg can precede the main administration.

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, 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
100 mg to 150 mg intravenously over 10 to 15 seconds, normally as a 2.5% w/v solution. A repeat dose of 100 mg to 150 mg may be given after one minute.

The intravenous injection should be given slowly and the amounts given titrated against the patient's response to minimise the risk of respiratory depression or the possibility of overdosage. The average dose for an adult of 70 kg is roughly 200 mg to 300 mg (8mls to 12 mls of a 2.5% w/v solution) with a maximum of 500 mg.

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

Elderly
Smaller adult doses are advisable (see section 4.4).

Method of administration
Administration of the drug is usually through a peripheral vein either at the elbow or back of the hand. It is recommended to administer incremental doses rather than one bolus dose in order to achieve greater control and better recovery.

Prior to administration of thiopental sodium, atropine or a similar agent may be administered to depress vagal reflexes and mucous secretions. Because thiopental sodium is a poor analgesic, narcotic analgesics may be given as part of the induction regimen.

Thiopental sodium may also be used for non-ventilated patients undergoing a short duration procedure. For these patients, supplementary doses should be given such as to maintain analgesia without excessive respiratory depression.

If administered rectally, thiopental sodium is given in doses of 25mg to 45mg per kg bodyweight dissolved in 25ml of water. Anaesthetic effects are usually seen within 10 minutes of administration.

(For instructions on dilution of the product before administration, see section 6.6.)

Use in convulsive states
75mg to 125mg (3mls to 5mls 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 bodyweight may be given to reduce elevations of intracranial pressure if controlled ventilation is provided.

Further information
Thiopental 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. (see sections 4.4 and 4.5)

Reduced doses are also indicated in patients who have been premedicated with narcotic analgesics. (see section 4.4)

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. (see section 4.4)

Reduced doses are recommended in patients with hepatic impairment, shock, dehydration, severe anaemia, hyperkalaemia, toxaemia, myxoedema or other metabolic disorders. (see section 4.4)

4.3 Contraindications

Thiopental sodium is contraindicated in respiratory obstruction, acute asthma, severe shock and dystrophia myotonica. Administration of any barbiturate is contraindicated in porphyria.

Patients with hypersensitivity or idiosyncratic reactions to barbiturates.

4.4 Special warnings and precautions for use

Thiopental sodium can cause respiratory depression, including apnoea, and a reduction in cardiac output, with a fall in blood pressure, 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, hypertension, 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, or other metabolic disorders e.g thyrotoxicosis, myxoedema and diabetes.

Use in hepatic and renal disease
Thiopental sodium is metabolised primarily in 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 (see also section 4.2 and 4.5) 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 long-term medications such as aspirin, oral anticoagulants, oestrogens, MAOIs and lithium may need to adjust the dose or stop therapy prior to elective surgery. Patient 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% 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 in-situ, 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 in neurological patients with raised intracranial pressure
Thiopental has been associated with reports of severe or refractory hypokalaemia during infusion; severe rebound hyperkalaemia may occur after cessation of thiopental infusion. The potential for rebound hyperkalaemia should be taken into account when stopping thiopental therapy.

This medicinal product contains53.5mg sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interactions

Thiopental sodium has been shown to interact with sulphafurazole (see also section 4.2 and 4.4).

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: Pre-treatment with aspirin has been shown to potentiate thiopental 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: Pre-treatment 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.

Herbal medicines: Animal data suggest valerian and St John’s Wort may prolong the effect of thiopental sodium.

Alcohol: The effect of alcohol may be increased in the period after treatment with thiopental sodium (for at least the first 24 hours).

4.6 Fertility, pregnancy and lactation

Breastfeeding
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.

Pregnancy

It has been shown that thiopental sodium can be used without adverse effects during pregnancy although the 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

Summary of the safety profile
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.

A fall in blood pressure is often seen when thiopental sodium is first given.

Although frequencies established in controlled clinical trials are not available for thiopental sodium, the following are known to be relatively common in patients post general anaesthesia: drowsiness; nausea, with or without vomiting; decreased appetite; malaise; fatigue; dizziness; headache; and delirium in elderly patients.

Excessive doses are associated with hypothermia and profound cerebral impairment.

Tabulated summary of adverse reactions
Adverse reactions from literature searches, post-marketing experience and spontaneous reports with thiopental sodium are listed in the table below.

Within the system organ class, the adverse reactions are listed by frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Adverse reaction	Frequency
Immune system disorder	Hypersensitivity, anaphylactic and anaphylactoid reactions	Not known
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyperkalaemia	Not known
Psychiatric disorders	Delirium, confusional state	Not known
Nervous system disorders	Cerebral impairment, amnesia, dizziness, somnolence, headache	Not known
Cardiac disorders	Myocardial depression, arrhythmia	Not known
Vascular disorders	Hypotension, circulatory collapse	Not known
Respiratory, thoracic and mediastinal disorders	Bronchospasm, respiratory depression, laryngospasm, cough, sneezing, apnoea	Not known
Gastrointestinal disorders	Nausea, vomiting	Not known
Skin and subcutaneous tissue disorders	Skin reaction	Not known
General disorders and administration site conditions	Malaise, fatigue, chills, extravasation, hypothermia	Not known
Investigations	Cardiac output decreased, blood pressure decreased	Not known

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRAPharmacovigilance,
Earlsfort Terrace,
IRL - Dublin 2;
Tel: +353 1 6764971;
Fax: +353 1 6762517.
Website: www.hpra.ie;
e-mail: medsafety@hpra.ie

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

Pharmacotherapeutic Group: Anesthetics, General; Barbiturates, Plain
ATC code: N01AF03

Thiopental sodium is a short acting substituted barbiturate, which 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 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 dependant 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 is strongly bound to plasma protein, which impairs excretion through the kidney. The metabolites are usually inactive and are then excreted. Thiopental therefore, whilst having a short duration of action, may have a long elimination phase.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Solution of Thiopental Sodium has a pH of 10 - 11 and are strongly alkaline in order to maintain stability. Solutions are incompatible with acid, acidic salts and solutions such as pethidine, morphine and promethazine.

This medicinal product should not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years.
After reconstitution: The product contains no preservative and should be used immediately. If stored before use, store upright between 2°C to 8°C and use within 7 hours. Use once following reconstitution and discard any residue.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton.

Store reconstituted solution between 2ºC to 8ºC in an upright position and use within 7 hours.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml Type III clear glass vials with 20 mm bromobutyl compound closures.

Pack sizes: 1, 10 and 25 vials per pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Solutions for administration are prepared by adding Water for Injection and shaking to dissolve the contents of the vial. The following guide may be followed:

	2.5% Solution 25mg per ml	**5% Solution 50mg per ml**
500mg vial	Add 20ml	Add 10ml

The recommended method of administration is by injection into the cannulated vein or by addition through the side arm of a peripheral intravenous infusion of sodium chloride 0.9% or dextrose 5% over the recommended period of time.

Solutions must be used within 7 hours of preparation, or discarded. Do not use if the solution is discoloured.

7 MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
Netherlands

8 MARKETING AUTHORISATION NUMBER

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