ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Thiopental Panpharma 0,5 g powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains thiopental sodium and sodium carbonate equivalent to 0,5 g thiopental sodium.

Excipient with known effect:
Each vial of Thiopental sodium 0,5 g contains 56 mg (2.5 mmol) sodium/vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection
Yellowish-white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous anaesthesia.
Induction of general anaesthesia and also as an adjunct to provide hypnosis during balanced anaesthesia with other anaesthetic agents, including analgesics and muscle relaxants.
As an adjunct for control of refractory convulsive disorders of various aetiology, including those caused by local anaesthetics.
Reducing the intracranial pressure in patients with increased intracranial pressure, if controlled ventilation is provided.

4.2 Posology and method of administration

Posology
Using of thiopental is reserved only for health care personnel trained in anaesthesiology. A person qualified in the use of anesthetics should be constantly available during the administration of the medicinal product.
After continuous administration of thiopental the effect duration is prolonged, personnel qualified in the use of anesthetics should be constantly available during the administration of the medicinal product.
A normal adult dose for induction of anaesthesia is 4-6 mg/kg body weight, but the 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, body weight and the patient's general condition. The dose should usually be reduced and carefully titrated in patients with a poor general condition. 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.

Test Dose
It is advisable to inject a small intravenous ''test'' dose of 25 to 75 mg (1 to 3 ml of a 2.5% solution) to assess tolerance or unusual sensitivity to thiopental and pausing to observe patient reaction for at least 60 seconds. If unexpectedly deep anesthesia develops or if respiratory depression occurs, consider these possibilities:
1. The patient may be unusually sensitive to thiopental.
2. The solution may be more concentrated than had been assumed.
3. The patient may have received too much premedication.

If the test dose results in local or regional pain, extravasal or intraarterial administration should be suspected (see section 4.4.).

Use in Anesthesia
Moderately slow induction can usually be accomplished in a healthy female or male adult weighing 60-80 kg by injection of 50 to 75 mg of thiopental at intervals of 20 to 40 seconds, depending on the reaction of the patient. Once anesthesia is established, additional injections of 25 to 50 mg can be given whenever the patient moves. Slow injection is recommended to minimize respiratory depression and the possibility of overdosage.
The smallest dose consistent with attaining the surgical objective is the desired goal. Momentary apnea following each injection is typical, and progressive decrease in the amplitude of respiration appears with increasing dosage. Pulse remains normal or increases slightly and returns to normal. Muscles usually relax about 30 seconds after unconsciousness is attained, but this may be masked if a skeletal muscle relaxant is used.
The tone of jaw muscles is a fairly reliable index. The pupils may dilate but later contract. Sensitivity to light is not usually lost until a level of anesthesia deep enough to permit surgery is attained. Nystagmus and divergent strabismus are characteristic during early stages, but at the level of surgical anesthesia, the eyes are central and fixed. Corneal and conjunctival reflexes disappear during surgical anesthesia.
When thiopental is used 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 infusion with a 0.2% or 0.4% concentration (see section 6.6). For information on preparation of solutions see section 6.6.
With continuous infusion, the depth of anesthesia is controlled by adjusting the rate of infusion.

Paediatric population

The doses are recommended for healthy paediatric population, and doses may have to be adjusted depending on for example concomitant illness, preanesthesia.

Newborns	IV 3 to 4 mg/kg then 1 mg/kg as needed
Infants	IV 5 to 8 mg/kg then 1 mg/kg as needed.
Children	IV 5 to 6 mg/kg then 1 mg/kg as needed.

The suggested paediatric dosage categories are only indicative of required doses. Actual dosing must be individualized and titrated to effect based on age, maturity and the general condition of the paediatric patient.

Use in convulsive states
75 mg to 125 mg (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.

Paediatric population
Intravenously 2 mg/kg initially and then individually titrated until satisfactorily clinical effect has been established. A maximum dose of 5 mg/kg/h should not be exceeded.

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.
Paediatric population
The safety of thiopental in paediatric populations to treat raised intracranial pressure has not yet been established.

Hepatic impairment
Reduced dose should be used in patients with hepatic impairment (see section 4.4).

Renal impairment
Thiopental should be used with caution in patients with renal impairment (see section 4.4).

Method of administration
This medicinal product must only be administered by the intravenous route. Care should be taken to ensure intravenous administration (see section 4.4). For instructions on dilution of the medicinal product before administration, see section 6.6. Infusion should only be given through a central venous catheter.

4.3 Contraindications

Hypersensitivity to barbiturates or to any of the excipients listed in section 6.1.
Thiopental is contra-indicated in respiratory obstruction, acute asthma, severe shock and dystrophia myotonica. Administration of any barbiturate is contra-indicated in porphyria.

4.4 Special warnings and precautions for use

Thiopental may cause addiction.
Keep endotracheal intubation equipment, oxygen and resuscitative equipment readily available.
Caution must be taken in patients with increased intracranial pressure or asthma.
If used under these conditions reduce dosage and administer slowly.

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.
Caution must be taken in patients with potential airway compromise, such as conditions involving inflammation in the mouth, jaw and throat.

Cardiorespiratory depression
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. Care should also be exercised with severe cardiovascular diseases, severe respiratory diseases and hypertension of various aetiology.

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, 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.

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.

Hepatic impairment
Thiopental sodium is metabolized primarily by the liver so doses should be reduced in patients with hepatic impairment.

Renal 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 in underlying disease
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. Patients with diabetes or hypertension may need to adjust their therapy before anaesthesia (see section 4.5).
Thiopental concentrations less than 2.0 % can cause hemolysis.

Extravascular infiltration:
Extravascular injection should be avoided. Care should be taken to ensure that the needle is within the lumen of the vein before intravenous injection of this medicinal product. Extravascular injection may cause chemical irritation of the tissues varying from slight tenderness to venospasm, extensive necrosis, severe pain 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% lidocaine locally to relieve pain and enhance vasodilatation. Local application of heat also may help to increase local circulation and removal of the infiltrate (see section 4.8).

Intra-arterial injection:
Intra-arterial injection can occur inadvertently, especially if an aberrant superficial artery is present at the medial aspect of the antecubital fossa. The area selected for intravenous injection of the drug should be palpated for detection of an underlying pulsating vessel. Accidental intra-arterial injection may 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. Methods suggested for dealing with this complication vary with the severity of symptoms (see section 4.8).

The following have been suggested (controlling investigations are missing):
1. Dilute the medicinal product by removing the tourniquet and any restrictive garments.
2. Leave the intravenous cannula in place, if possible.
3. Inject the artery with a dilute solution of papaverine, or lidocaine, 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, treat with heparin 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.

This medicinal product contains 56 mg (or 2.5 mmol) sodium per dose of 0,5 g vials equivalent to 2.8 % (0,5 g vial) of the WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
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.

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

Benzodiazepines: Midazolam potentiates the anaesthetic effects of thiopental sodium.

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

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.

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

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

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.

Vasodilator antihypertensives: Enhanced hypotensive effect when general anaesthetics given with hydralazine, minoxidil or nitroprusside.
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 neuron blockers: Enhanced hypotensive effect when general anaesthetics given with adrenergic neurone blockers.

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

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

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.
Opioids potentiate the respiratory depressive effect. The effect is enhanced by alcohol, hypnotics, central acting muscle relaxants, anxiolytics, antipsycotics and antihistamines.
Thiopental interacts with opioid analgesics (decreased sensibility to pain) and sufentanile (decrease dose dependently the need of barbiturates at induction of anaesthesia. Increased doses may be necessary in patients with alcohol- or narcotics misuse.

Pharmacokinetic interactions
Concomitant use of barbiturates and quetiapine may result in a reduced serum concentration of quetiapine.

Barbiturates increase by enzyme induction the elimination of androgens, some antiepileptics, felodipin, glucocorticoids, metronidazole, peroral anticoagulants and estrogen and thereby decrease the plasma concentration of these substances.
Barbiturates inhibit the hypoglycaemic effect of peroral antidiabetics (sulfonyl-urine substances).
Barbiturates inhibit the effect of bronchodilators (aminophylline).

4.6 Fertility, pregnancy and lactation

Pregnancy
It has been shown that thiopental can be used without adverse effects during pregnancy. However, when considering use of thiopental the clinician should only use the drug when the expected benefits outweigh any potential risks.
Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding
Thiopental readily crosses the placental barrier and also appears in breast milk. Therefore, breast-feeding should be temporarily suspended (for at least 12 hours) or breast milk expressed before the induction of anaesthesia.

Fertility
There are no data on the effect of thiopental on human fertility.

4.7 Effects on ability to drive and use machines

This medicinal product has major influence on the ability to drive and use machines. Even though the recovery after use of this medicinal product is rapid; post-operative vertigo, disorientation and sedation may be prolonged and out-patients given thiopental should therefore be advised not to drive or use machinery especially within the first 24 to 36 hours.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following:
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), not known (cannot be estimated from the available data).

System Organ Class	**Common (≥1/100 to <1/10)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known (cannot be estimated from the available data)**
Cardiac disorders	Heart arrhythmia, Myocardia depression, Hypotension		
Nervous system disorders	Somnolence, Delayed wakening		Headache, Dizziness
Respiratory, thoracic and mediastinal disorder	Respiratory depression, Bronchospasm, Laryngospasm, Coughing, Snoring		
General disorders and administration site conditions	Shivering	Anaphylactoid reactions (urticaria, bronchospasm, fall in blood pressure and angioedema)	Malaise, Fatigue
Metabolism and nutrition disorders			Hypokalaemia, Hyperkalaemia,

System Organ Class	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
			Anorexia
Immune system disorders			Allergic reactions, Skin reactions, Hypersensitivity Anaphylactic reaction

Immune hemolytic anemia with renal failure and paralysis of nervus radialis have been reported in rare cases. Reactions which may be caused by the diluent, preparation – or solving technique or by administration of prepared solutions with thiopental sodium include fever, venous thrombosis or phlebitis at the injection site, and events after extravasal injection.
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
Postoperative vomiting is infrequent, but shivering may occur and there may be persistent drowsiness, confusion and amnesia.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Overdosage may occur from too rapid or repeated injections. Too rapid injection may be followed by an alarming fall in blood pressure and shock. Apnea may occur in connection with too excessive or too rapid injections. Also laryngospasm, coughing and other respiratory difficulties may occur, but may also be a sign of under dosing (reflex induced).

In the event of suspected or apparent overdosage, the drug should be discontinued. A patent airway should be secured. Oxygenation and ventilation should be monitored and supported as needed. The circulation should be monitored and supported as needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaceutical group: General anesthetics – Barbiturates plain,
ATC Code: N01AF03
This medicinal product is a thiobarbiturate with rapid onset for intravenous administration. Thiopental induces hypnosis and anesthesia, but not analgesia. Hypnosis is produced within 30 to 40 seconds. Recovery is within 30 minutes after adequate induction dose. Repeated injections give a prolonged anesthesia because of entry into fatty tissue.
Thiopental 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 is almost completely metabolized and only approximately 0.3 % is excreted unchanged in the urine. Thiopental is extremely fat soluble and is largely metabolized in the liver but is slowly excreted from lipid depot and is very slowly transformed. During one hour 10-15 % is metabolized, mainly in the liver. The half-life of the distribution phase after a single intravenous dose is 2-4 hours and the half-life of the elimination phase is 9-11 hours. The plasma protein binding is 80-90% at therapeutic concentration level.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate.

6.2 Incompatibilities

This medicine must not be mixed with other medicinal products except those mentioned in section 6.6.
The solutions prepared with THIOPENTAL are strongly alkaline and are not compatible with volume replacement solutions and acidic anaesthetic adjuvant solutions, since precipitation and clogging of the injection needle may occur. Similarly, chemical changes in the added solution cannot be ruled out.

The stability of this medicine solution 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 this medicine solution will increase the likelihood of precipitation of thiopental acid. Such factors include the use of diluents which are too acidic and the absorption of carbon dioxide which can combine with water to form carbonic acid.

Solutions of suxamethonium, tubocurarine or other drugs which have an acid pH should not be mixed with this medicine solution.

The most stable solutions are those reconstituted in sterile water and/or isotonic sodium chloride.

6.3 Shelf life

3 years
Shelf-life after reconstitution
Chemical and physical in-use stability has been demonstrated for 9 hours below 25°C and 24 hours at 2°C to 8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 mL vials made from colourless glass with a bromobutyl rubber stopper, aluminium seal and a polypropylene flip-off cap.
Pack size: 1, 10, 25 and 50 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Solutions should be prepared aseptically with one of the following diluents:
- Sterile Water,
- Sodium chloride (9 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 injection is isotonic; concentrations less than 2.0% in this diluent are not used because they cause hemolysis. For continuous intravenous drip administration, concentrations of 0.2% or 0.4% are used. Solutions may be prepared by adding thiopental to 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 this medicinal product 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**.** Sterilization by vapour should not be attempted.

For single use after reconstitution. Discard any remainder after use.

Any solution of this medicine with a visible precipitate should not be administered.

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF THE TEXT

2023.02.03