

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Thiotepa 15mg Powder for Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 15mg Thiotepa. When reconstituted as directed, the resulting solution contains 10mg/ml of Thiotepa.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
A sterile, white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Thiotepa (N, N', N'' triethylenethiophosphoramidate) is a polyfunctional alkylating agent used alone or in combination with other cytotoxic drugs, or with surgery in the treatment of neoplastic diseases.

4.2 Posology and method of administration

Thiotepa (15mg) should be aseptically reconstituted with 1.5ml Water for Injection immediately prior to use. Please refer to specific sections on particular disease types for further reconstitution instructions. Reconstituted solutions should be clear to slightly opaque. Solutions that are grossly opaque or precipitated should be discarded.

Use Luer-Lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

Thiotepa may be given by intravenous, intramuscular and intrathecal routes of injection; it may be given directly into pleural, pericardial or peritoneal cavities and as a bladder instillation.

Since absorption from the gastrointestinal tract is variable, Thiotepa should not be administered orally. Dosage must be carefully individualised. A slow response to Thiotepa does not necessarily indicate a lack of effect. Therefore, increasing the frequency of dosing may only increase toxicity.

For intramuscular injection, bladder and intracavitary instillations:

Dosage: Adults, Adolescents over 12 years and the elderly

Up to 60mg in single or divided doses. Doses should be reduced in cases of leucopenia as indicated in Table 1. Single dose administration of 90mg Thiotepa as a bladder instillation is described under "Bladder Cancer".

WBC Count Cells/mm ³	Dose of Thiotepa Adults and Adolescents over 12 years
6000	60 mg
5000-6000	45 mg
4500-5000	30 mg
4000-4500	20 mg
3500-4000	10 mg
3000-3500	5 mg
below 3000	omit dose

Intravenous Injection: Half of the above adult dose.

Children: Use in children is not recommended.

Intrathecal injection: Up to a maximum of 10mg.

It is essential that a complete blood count should be performed 12-24 hours before each dose of Thiotepa. Thrombocytopenia in the absence of leucopenia has been noted.

Dosage schedules of Thiotepa vary widely according to the route of administration and the indication.

Examples of dosage schedules used according to specific tumour types are given below:

Breast Cancer:

Patients with advanced breast cancer have been treated with Thiotepa as part of a combination regime, given intramuscularly in divided doses of 15-30mg three times weekly for two weeks; this representing one course of treatment. An interval of six to eight weeks is recommended between courses to allow bone marrow recovery.

An alternative schedule employs Thiotepa as part of a combination regime, given as an initial priming dose of 15mg intramuscularly or intravenously each day for four days. This may be followed in three weeks by maintenance doses of 15mg I.M. every 14-21 days.

Bladder Cancer:

Instillations of Thiotepa have been used to treat multiple superficial tumours of the bladder, resulting in a complete clinical response in about one third of patients. Patients are dehydrated for 8-12 hours prior to treatment. Up to 60mg Thiotepa dissolved in 60ml sterile water is instilled into the bladder by catheter once a week for four weeks. During removal of the catheter following instillation, Thiotepa injection is continued to ensure bathing of the prostatic and pendulous urethra. The solution should be retained for up to two hours and the patient should be frequently repositioned to ensure maximum contact with the urothelium.

Patients are generally cystoscoped two weeks after a course of four instillations. If a response is observed a second course of four Thiotepa instillations may be given, generally at a reduced dosage, e.g. 15-60mg with intervals of one to two weeks between instillations.

Second and third courses must be given with caution since bone-marrow depression may be increased. Deaths have occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

Instillations of Thiotepa have been used prophylactically as an adjunct to surgical resection of superficial tumours of the bladder, resulting in a marked decrease in the recurrence rate. It is recommended that there should be a minimum interval of one week between tumour resection and the commencement of prophylactic instillation of Thiotepa. 30-60mg Thiotepa dissolved in 60ml sterile water is instilled into the bladder for two hours and repeated at intervals of one to two weeks for a total of 4-8 instillations. This initial course may be followed by instillations of Thiotepa, 30-60mg every four to six weeks for one year or longer.

Single dose Thiotepe instillations have been used prophylactically as an adjunct of surgical resection in the treatment of superficial tumours of the bladder. 90mg Thiotepe dissolved in 100mg sterile water is instilled into the bladder with the patient in the left lateral position. After 15 minutes the patient is transferred to the right lateral position and after a further 15 minutes the bladder is emptied. It is felt that such single dose administration may decrease the incidence of systemic toxicity by decreasing the extent of systemic absorption of the drug.

Note: Patients who have had previous radiotherapy to the bladder are at increased risk of drug toxicity.

Malignant meningeal disease:

Intrathecal injections of Thiotepe have been found to be useful for the palliative treatment of cases of meningeal infiltration by leukaemia and lymphoma. Clinical experience has shown Thiotepe to be effective in carcinomatous involvement of the meninges, but published data is limited.

Thiotepe, at a concentration of 1mg/ml in sterile water is administered by injection through a lumbar theca in doses of up to 10mg on alternate days until there is clearance of malignant cells from the cerebrospinal fluid (CSF). It is recommended that if no improvement occurs in the CSF after three injections, then treatment should be changed. Not more than four injections should be given on alternate days. Routine blood counts should be performed prior to each dose of Thiotepe.

Ovarian cancer

Ovarian cancer has been treated with Thiotepe as a single agent or as part of a combination regime in a variety of schedules. For example, 15mg Thiotepe I.V. or I.M. may be given daily for four days initially and then continued with single doses administered once a week or once every two weeks.

Intracavitary instillation of Thiotepe:

Instillations of Thiotepe have been used to treat malignant pleural effusions and abdominal ascites. The procedure recommended, is first to aspirate as much fluid as possible and then to instil the dose of Thiotepe, 10-60mg in 20-60ml sterile water. This may be repeated once a week or once every two weeks.

Prevention of recurrences of Pterygium

A 1:2,000 solution of Thiotepe in sterile Ringer's solution (i.e. 15mg powder in 30ml Ringer's), applied topically as eye drops, every three hours daily for up to six weeks after surgical removal of the pterygium, is effective in reducing the recurrence rate following surgery.

Condyloma Acuminata:

Thiotepe applied topically or instilled intraurethrally in a gel, has been successfully used to eradicate condyloma acuminata. The drug may be administered by first reconstituting 60mg Thiotepe with 5ml sterile water. This is diluted to 15ml, using a sterile mixture of water and lubricating jelly made to a consistency viscous enough to remain in the urethra and fluid enough to allow easy injection. This therapy may be repeated at weekly intervals.

4.3 Contraindications

Thiotepe administration is contraindicated in patients with a WBC count below 3,000 and/or a platelet count below 100,000 and in patients with known hypersensitivity to ingredients of this preparation.

4.4 Special warnings and precautions for use

Death from septicaemia and haemorrhage has occurred as a direct result of haematopoietic depression by Thiotepe. Death has also occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

Thiotepa should only be administered under the direction of a specialist oncology service having the facilities for regular monitoring of clinical biochemical and haematological effects during and after administration. Thiotepa is highly toxic to the haematopoietic system. WBC and platelet counts are recommended 12-24 hours before each dose of Thiotepa, at weekly intervals during therapy, and for at least three weeks after therapy has been discontinued, regardless of route of administration, except when used topically as eye drops or in the treatment of condyloma acuminata. Bone marrow depression may be delayed; the nadir in blood cell and platelet counts may occur up to 30 days after treatment is stopped. Myelosuppression has occasionally been prolonged.

Dosage should be reduced or discontinued in the presence of a compromised bone marrow, as manifested by a rapidly falling WBC count or platelet count. Dosage should be adjusted according to WBC count (see table 1, *Section 4.2, Posology and Method of Administration*). Thiotepa administration is contra-indicated in patients with WBC count below 3,000 and/or platelet count below 100,000 (see *Section 4.3, Contra-indications*). Treatment should be discontinued if the white cell or platelet count falls rapidly.

Thiotepa should in general not be used in patients with existing hepatic, renal or bone marrow damage and only if the need outweighs the risk in such patients. The lowest effective dosage should be used with hepatic, renal and haematopoietic function tests.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreasing hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Safe use in children has not been established.

Effective contraception should be used during Thiotepa therapy if either the patient or the partner is of childbearing potential (see *Section 4.6, Pregnancy and Lactation* and *Section 5.3, Preclinical safety data*).

Thiotepa may be mixed in the same syringe with procaine hydrochloride 2% or with adrenaline 1 in 1,000 or with both.

Trained personnel should reconstitute Thiotepa in a designated area. Caution should be exercised in the handling and preparation of Thiotepa. Adequate protective gloves and goggles should be worn and the work surface should be covered with plastic-backed absorbent paper. Thiotepa is not a vesicant and should not cause harm if it comes in contact with the skin. It should, of course, be washed off with water immediately. If Thiotepa contacts mucous membranes, the membranes should be flushed thoroughly with water. Any transient stinging may be treated with bland cream. The cytotoxic preparation should not be handled by pregnant staff.

Any spillage or waste material may be disposed of by incineration. We do not make any specific recommendations with regard to the temperature of the incinerator.

Thiotepa has been reported to possess mutagenic activity on the basis of bacterial, plant and mammalian mutagenicity tests. It has also been reported to be carcinogenic in mice and rats. These effects are consistent with its activity as an alkylating agent. There is some evidence of carcinogenicity in man. In patients treated with Thiotepa, cases of myelodysplastic syndromes and non-lymphocytic leukaemia have been reported.

4.5 Interaction with other medicinal products and other forms of interaction

It is not advisable to combine, simultaneously or sequentially, cancer chemotherapeutic agents or a cancer chemotherapeutic agent and a therapeutic modality having the same mechanism of action. Therefore, Thiotepa combined with other alkylating agents such as nitrogen mustard or cyclophosphamide or Thiotepa combined with irradiation would serve to intensify toxicity rather than to enhance therapeutic response. If these agents must follow each other, it is important that recovery from the first agent, as indicated by white blood cell count, be complete before therapy with the second agent is instituted.

Other drugs which are known to produce bone-marrow depression should be avoided.

Prolonged apnoea has been reported when succinylcholine was administered prior to surgery, following combined use of Thiotepea and other anticancer agents. It was theorised that this was caused by decrease of pseudocholinesterase activity caused by anticancer drugs.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Patients of childbearing potential should be advised to avoid pregnancy.
The drug therefore, should not be administered to patients who are pregnant or to mothers who are breast feeding unless the benefit outweighs the risk to the foetus or child.

If Thiotepea is used during pregnancy, or if pregnancy occurs during Thiotepea therapy, the patient and partner should be apprised of the potential hazard to the foetus. (see *section 5.3, Preclinical safety data*)
There are no data on the excretion of Thiotepea in human breast milk. Breast feeding should be discontinued during and for three months following the use of Thiotepea.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

The most serious side-effect is upon the blood forming elements and is a direct consequence of the cytotoxic effect of the drug. Death from septicaemia and haemorrhage has occurred as a direct consequence of haematopoietic suppression.

Infections and Infestations	Increased susceptibility to infections.
Neoplasms benign and malignant (including cysts and polyps)	Myelodysplastic syndrome, acute non-lymphocytic leukaemia.
Blood and lymphatic system disorders	Bone marrow depression, thrombocytopenia, haematopoietic suppression.
Immune system disorders	Allergic reactions.
Metabolism and nutrition disorders	Anorexia.
Nervous system disorders	Headache, dizziness.
Eye disorders	Depigmentation of periorbital skin after using Thiotepea eyedrops, blurred vision, conjunctivitis.
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain.
Skin and subcutaneous tissue disorders	Rash, contact dermatitis, alopecia.
Renal and urinary disorders	Haemorrhagic cystitis after intravesical or intravenous administration, dysuria, urinary retention.
Reproductive system and breast disorders	Impairment of fertility, amenorrhoea, interference with spermatogenesis.

General disorders and administration site conditions

Fatigue, weakness, febrile reaction, pain at injection site, skin discolouration following topical use or exposure, local irritation comparable to mild radiation cystitis following bladder instillations.

4.9 Overdose

There is no specific antidote. General supportive measures are recommended. Thiotepa may be removed using dialysis. Blood counts should be carried out to estimate damage to the haematopoietic system. Whole blood, platelet, or leucocyte transfusions have proven beneficial.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Alkylating Agents – Ethylene imines
ATC Code: L01A C01

Thiotepa (N, N', N'' triethylenethiophosphoramidate) is an ethyleneimine compound whose antineoplastic effect is related to its alkylating action. It is believed to exert its cytotoxic effects by the alkylation of DNA. It is not a vesicant and may be given by all parenteral routes, as well as directly into tumour masses.

5.2 Pharmacokinetic properties

Variable absorption occurs from intramuscular injection sites. Absorption through serous membranes such as the bladder and pleura occurs to some extent. Only traces of unchanged Thiotepa and triethylene phosphoramidate are excreted in the urine, together with a large proportion of metabolites.

5.3 Preclinical safety data

Thiotepa has been shown to be mutagenic in various in vitro assays, and carcinogenic in animal studies.

Thiotepa is teratogenic and embryotoxic in mice and rats following intraperitoneal administration (see *Section 4.6, Pregnancy and Lactation*). In addition, it has been reported to interfere with spermatogenesis and ovarian function in rodent species.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

None

6.2 Incompatibilities

None known.

6.3 Shelf Life

Dry Powder as packaged for sale: 18 months.

6.4 Special precautions for storage

Store in a refrigerator (at 2°C-8°C). Do not freeze. Store in the original package. When aseptically reconstituted the product may be kept in a refrigerator (2°C - 8°C) for up to 24 hours.

6.5 Nature and contents of container

2ml Type I flint glass vial with butyl rubber stopper.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Thiotepa (15mg) should be aseptically reconstituted with 1.5ml water for Injections immediately prior to use. Reconstituted solutions should be clear to slightly opaque. Solutions that are grossly opaque or precipitated should be discarded.

For single use only. Discard any unused contents.

Handling of cytotoxic drugs

Please consult any local guidelines on the handling of cytotoxic drugs before commencing. Trained personnel should reconstitute Thiotepa in a designated area. Adequate protective gloves and goggles should be worn and the work surface should be covered with disposable plastic-backed absorbent paper.

Care should be taken to avoid the drug accidentally coming into contact with the eyes. Thiotepa is not vesicant and should not cause harm if it comes into contact with the skin. Any contamination of the skin or eyes should immediately be thoroughly washed with water. Any transient stinging may be treated with bland cream

The cytotoxic preparation should not be handled by pregnant staff.

Any spillage or waste material may be disposed of by incineration. We do not make any specific recommendations with regards to the temperature of the incinerator.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0899/025/001

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