PRESCRIBING INFORMATION

THIOTEPA
(Thiotepa)

Sterile Powder for Injection

Cytotoxic Agent

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COMPLETE PRESCRIBING INFORMATION

THIOTEPA

Sterile Thiotepa Cryodesiccated Powder for Injection

Cytotoxic Agent

CLINICAL PHARMACOLOGY

THIOTEPA is a cytotoxic agent of the polyfunctional alkylating type (more than one reactive ethylenimine group) related chemically and pharmacologically to nitrogen mustard. Its radiomimetic action is believed to occur through the release of ethylenimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines.

On the basis of tissue concentration studies, it is reported that THIOTEPA has no differential affinity for neoplasms. Thiotepa and triethylenephosphoramide (TEPA) in urine each accounts for less than 2% of the administered dose.

INDICATIONS AND CLINICAL USE

THIOTEPA has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:

1. Adenocarcinoma of the breast.
2. Adenocarcinoma of the ovary.

3. For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.

4. For the treatment of superficial papillary carcinoma of the urinary bladder.

While now largely superseded by other treatments, THIOTEPA has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.

CONTRAINDICATIONS

Therapy is probably contraindicated in cases of existing hepatic, renal, or bone marrow damage. However, if the need outweighs the risk in such patients, THIOTEPA may be used in low dosage, and accompanied by hepatic, renal and hemopoietic function tests.

THIOTEPA is contraindicated in patients with a known hypersensitivity (allergy) to this preparation.

WARNINGS

The administration of THIOTEPA to pregnant women is not recommended except in cases where the benefit to be gained outweighs the risk of teratogenicity involved.

Death has occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

THIOTEPA is highly toxic to the hematopoietic system. A rapidly falling white blood cell or platelet count indicates the necessity for discontinuing or reducing the dosage of THIOTEPA. Weekly blood and platelet counts are recommended during therapy and for at least three weeks after therapy has been discontinued. 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.

THIOTEPA is a polyfunctional alkylating agent, capable of cross-linking the DNA within a cell and changing its nature. The replication of the cell is, therefore, altered, and THIOTEPA may be described as mutagenic. An in vitro study has shown that it causes chromosomal aberrations of the chromatid type and that the frequency of induced aberrations increases with the age of the subject.

Like many alkylating agents, THIOTEPA has been reported to be carcinogenic when administered to laboratory animals. Carcinogenicity is shown most clearly in studies using mice but there is strong circumstantial evidence of carcinogenicity in man. In patients treated with THIOTEPA, cases of myelodysplastic syndromes and acute non-lymphocytic leukemia have been reported.

PRECAUTIONS

The serious complication of excessive THIOTEPA therapy, or sensitivity to the effects of THIOTEPA, is bone marrow depression. If proper precautions are not observed THIOTEPA may cause leukopenia, thrombocytopenia, and anemia. Death from septicemia and hemorrhage has occurred as a direct result of hematopoietic depression by THIOTEPA.

The patient should notify the physician in the case of any sign of bleeding (epistaxis, easy bruising, change in colour of urine, black stool) or infection (fever, chills) or for possible pregnancy to patient or partner. Effective contraception should be used during THIOTEPA therapy if either the patient or the partner is of childbearing potential. THIOTEPA can cause fetal harm when administered to a pregnant woman. THIOTEPA impaired fertility, inhibited implantation and interfered with spermatogenesis in animal studies. There are no adequate and well-controlled studies in pregnant women. If THIOTEPA is used during pregnancy, or if pregnancy occurs during THIOTEPA therapy, the patient and partner should be apprised of the potential hazard to the fetus.

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

The most reliable guide to THIOTEPA toxicity is the white blood cell count. If this falls to 3000/mm^3 or less, the dose should be discontinued. Another good index of THIOTEPA toxicity is the platelet

count; if this falls to 150,000/mm^3, therapy should be discontinued. Red blood cell count is a less accurate indicator of THIOTEPA toxicity.

White blood cell counts and platelet counts are recommended 12-24 hours before each dose of THIOTEPA, and weekly during therapy and for at least 3 weeks after therapy has been discontinued. Dosage should be reduced in the presence of compromised bone marrow as manifested by a reduced WBC or platelet count (See WARNING).

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

If the drug is used in patients with hepatic or renal damage (see CONTRAINDICATIONS Section), regular assessment of hepatic and renal function tests are indicated.

There is no known antidote for overdosage with THIOTEPA. Transfusions of whole blood or platelets or leukocytes have proved beneficial to the patient in combatting hematopoietic toxicity.

Nursing Mothers

It is not known whether THIOTEPA is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for THIOTEPA in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of THIOTEPA did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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.

ADVERSE REACTIONS

In addition to its effect on the blood-forming elements, (see WARNINGS and PRECAUTIONS Sections), THIOTEPA may cause other adverse reactions.

General: Fatigue, weakness. Febrile reaction and discharge from a subcutaneous lesion may occur as the result of breakdown of tumor tissue.

Carcinogenecity Studies: THIOTEPA has been shown to be mutgenic in various in vitro assays, and carcinogenic in animal studies.

Hypersensitivity Reactions: Allergic reactions - rash, urticaria, laryngeal edema, asthma, anaphylactic shock, wheezing.

Local Reactions: Contact dermatitis, pain at the injection site.

Gastrointestinal: Nausea, vomiting, abdominal pain, anorexia.

Renal: Dysuria, urinary retention. There have been rare reports of chemical cystitis or hemorrhagic cystitis following intravesical, but not parenteral administration of THIOTEPA.

Respiratory: Prolonged apnea has been reported when succinylcholine was administered prior to surgery, following combined use of THIOTEPA and other anticancer agents. It was theorized that this was caused by decrease of pseudocholinesterase activity caused by the anticancer drugs.

Neurologic: Dizziness, headache, blurred vision.

Skin: Dermatitis, alopecia. Skin depigmentation has been reported following topical use.

Special Senses: Conjunctivitis.

Reproductive: Amenorrhea, interference with spermatogenesis.

Infections: Increased susceptibility to infections.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Hematopoietic toxicity can occur following overdose, manifested by a decrease in the white cell count and/or platelets. Red blood cell count is a less accurate indicator of THIOTEPA toxicity. Bleeding manifestations may develop. The patient may become more vulnerable to infection, and less able to combat such infection.

Dosages within and minimally above the recommended therapeutic doses have been associated with potentially life-threatening hematopoietic toxicity. THIOTEPA has a toxic effect on the hematopoietic system that is dose related.

THIOTEPA is dialyzable.

There is no known antidote for overdosage with THIOTEPA. Gastric lavage , forced fluids, and general supportive measures are recommended. Transfusions of whole blood or platelets have proven beneficial to the patient in combating hematopoietic toxicity.

DOSAGE AND ADMINISTRATION

Parenteral routes of administration are most reliable since absorption of THIOTEPA from the gastrointestinal tract is variable.

Since absorption from the gastrointestinal tract is variable, THIOTEPA should not be administered orally.

Since THIOTEPA is nonvesicant, intravenous doses may be given directly and rapidly without need for slow drip or large volumes of diluent.

Dosage must be carefully individualized. A slow response to THIOTEPA may be deceptive and may occasion unwarranted frequency of administration with subsequent signs of toxicity. After maximum benefit is obtained by initial therapy, it is necessary to continue the patient on maintenance therapy (1 to 4 week intervals). In order to continue optimal effect, maintenance doses should be no more frequent than weekly in order to preserve correlation between dose and blood counts.

Initial and Maintenance Doses: Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts.

Intravenous Administration: THIOTEPA may be given by rapid intravenous administration in doses of 0.3 - 0.4 mg/kg. Doses should be given at 1 to 4 week intervals.

For conversion of mg/kg of body weight to mg/M^2 of body surface or the reverse, a ratio of 1:30 is given as a guideline. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Intracavitary Administration: The dosage recommended is 0.6 - 0.8 mg/kg. Administration is usually effected through the same tubing which is used to remove the fluid from the cavity involved.

Intravesical Administration: Patients with papillary carcinoma of the bladder are dehydrated for 8 to 12 hours prior to treatment. Then 60 mg of THIOTEPA in 30 - 60 mL of 0.9% Sodium Chloride Injection is instilled into the bladder by catheter. For maximum effect, the solution should be retained for 2 hours.

If the patient finds it impossible to retain 60 mL for 2 hours, the dose may be given in a volume of 30 mL. If desired, the patient may be positioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but 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.

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

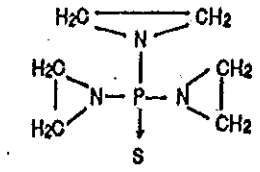
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: THIOTEPA

Chemical name: 1, 1', 1" - phosphinothioylidynetris-aziridine

Structural Formula:



Molecular formula: $C_6H_{12}N_3PS$

Molecular weight: 189.22

Description: THIOTEPA is a powder stable in alkaline medium and unstable in acid medium. When the lyophylized powder formulation is reconstituted with Sterile Water for Injection, the resulting solution has a pH of approximately 5.5 - 7.5.

COMPOSITION

THIOTEPA 15 mg/vial is a non-pyrogenic sterile lyophilized powder that contains no non-medicinal ingredients.

STABILITY AND STORAGE RECOMMENDATIONS

When in its original powder form, THIOTEPA must be stored in the refrigerator at 2-8EC (36-46EF). Protect from light.

RECONSTITUTED SOLUTIONS

The powder should be reconstituted preferably in Sterile Water for Injection. The amount of diluent most often used is 1.5 mL resulting in a drug concentration of 5 mg in each 0.5 mL of solution. The reconstituted solution is hypotonic and should be further diluted with 0.9% Sodium Chloride Injection before use.

When reconstituted with Sterile Water for Injection, solutions of THIOTEPA should be stored in a refrigerator and used within 8 hours. Reconstituted solutions further diluted with 0.9% Sodium Chloride Injection should be used immediately.

In order to eliminate haze, solutions should be filtered through a 0.22 micron filter* prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used.

*Polysulfone membrane (Gelman's Sterile Aerodisc7, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore's MILLEX7-GS Filter Unit).

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

Larger volumes are usually employed for intracavitary use, intravenous drip, or perfusion therapy. The 1.5 mL reconstituted preparation may be added to larger volumes of 0.9% Sodium Chloride Injection, USP . Reconstituted solutions should be clear to slightly opaque but solutions that are grossly opaque or precipitated should not be used.

PARENTERAL PRODUCTS

The actual withdrawable quantities and concentration achieved are illustrated in the following table:

Label Claim (mg/vial)	Actual Content (mg/vial)	Amount of Diluent to be Added (mL)	Approximate Withdrawable Volume (mL)	Approximate Withdrawable Amount (mg/vial)	Approximate Reconstituted Concentration (mg/mL)
15.0	15.6	1.5	1.4	14.6	10.4

SPECIAL INSTRUCTIONS

Preparation and Administration Precautions: THIOTEPA is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling and preparation of THIOTEPA. Skin reactions associated with accidental exposure to THIOTEPA may occur. The use of

gloves is recommended. If THIOTEPA solution contacts the skin, immediately wash the skin thoroughly with soap and water. If THIOTEPA contacts mucous membranes, the membranes should be flushed thoroughly with water.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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. THIOTEPA is not vesicant and should not cause harm if it comes in contact with the skin. It should, of course, be washed off with water immediately. Any transient stinging may be treated with a bland cream.

The cytotoxic preparation should not be handled by pregnant staff.

AVAILABILITY OF DOSAGE FORMS

THIOTEPA, for single use only, is available in 15 mg vials, as sterile lyophilized powder for parenteral use after reconstitution and further diluted with 0.9% Sodium Chloride Injection before use.

Product Code: 8037

Available in boxes of 10 vials.

PHARMACOLOGY

Pharmacokinetics

THIOTEPA (TTPA) is poorly absorbed from the gastrointestinal tract, but it is non-irritant, and therefore it can be administered by the IM, IV, and IA routes. It has also been given by intrathecal, intravesicular, and intracavitary routes, and by regional perfusion.

TTPA is only poorly absorbed into the system following irrigation of the normal bladder (19.5%), but the degree of absorption increases with increased pathology of the urothelium. Table 1 shows the absorption of TTPA used in a concentration of 60 mg in 60 mL for bladder irrigation.

TABLE 1. ABSORPTION OF TTPA VIA THE BLADDER

	Absorption	
	mg	(%)
Normal bladder	11.7	(19.5)
Small bladder tumor	23.9	(39.8)
Large bladder tumor	38.5	(64.2)
Cystitis	47.6	(79.3)
Small tumor after TUR	54.6	(91.0)
Disseminated papillomatosis	58.5	(97.5)

Peak plasma levels were observed at 1.0 hour postirrigation and remained high (as much as 30 mcg/mL) for up to 5 hours. It is probable, however, that these plasma levels represent metabolites of THIOTEPA, because the assay methods used in this study were not highly selective.

When TTPA was administered at a dosage of 12 mg/m^2 by IV bolus, the plasma concentrations declined in a biexponential fashion; $T_{1/2}$ [alpha] = 7.5 $\pm$ 1.6 min, $T_{1/2}$ [beta] = 109 $\pm$ 21 min; total body clearance of TTPA was 140 $\pm$ 18 mL/min/m^2. The V_D was 9.6 $\pm$ 1.8 L/m^2, and V_{SS} was 23.6 $\pm$ 3.8 L/m^2.

TTPA is rapidly metabolized to triethylenephosphoramide (TEPA); by 15-30 minutes, plasma TEPA concentrations exceed those of TTPA, and persist in plasma much longer than TTPA. Very little TTPA is excreted in urine over 24 hours, but the metabolite (TEPA) accounts for approximately 15% of the administered dose.

TOXICOLOGY

Hematologic Toxicity

The major dose-limiting toxicity of THIOTEPA (TTPA) is myelosuppression. This usually results in reduced granulocyte counts, or thrombocytopenia, and occasionally anemia. In severe cases, it can result in pancytopenia, serious infections, and death; therefore, blood samples must be monitored prior to therapy and before each drug cycle, and the dose of TTPA adjusted accordingly (Table 2). It should be noted that other dosage schedules have been proposed in the medical literature. The degree of myelosuppression and the time to nadir are influenced by many factors including dosage and route of administration, patient performance status, prior therapy, bone marrow reserves, and specific disease.

Depression of WBC counts occurs within 5-30 days after a 5-7 day course, with the nadir usually at about 14 days.

Recovery from marrow toxicity usually occurs within 30 days, but occasionally may take 6-8 weeks. Thrombocytopenia usually occurs later than granulocytopenia, but there is no consistent pattern; and some investigators note that thrombocytopenia is frequently associated with prolonged drug administration, and can occur even when WBC counts are not seriously depressed.

TABLE 2. WBC TOXICITY AND DOSAGE

ADJUSTMENTS OF TTPA

WBC Count/mm^3	Dose of TTPA Adults & Children 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 dosage

Myelosuppression can also occur following intravesicular administration of TTPA, therefore it is important to monitor blood samples of all patients receiving substantial doses of TTPA.

There have been rare reports of "chronic" myelosuppression and refractory anemia with excess blast forms in patients who have received large quantities of TTPA (up to 2,286 mg over 53 months). There have been 2 accounts of leukemia that might be drug related.

Other Toxicities

Other systemic toxicities include nausea and vomiting which tend to be mild and insignificant. Alopecia is a rare occurrence. Some CNS toxicity has been observed following intrathecal drug administration. Dysuria, hematuria, and bladder irritation may accompany the intravesicular administration of TTPA.

There have been occasional reports of skin reactions to TTPA therapy, but it must be noted that some of these patients were receiving combination drug regimens. There have been 3 cases reported of depigmentation around the eye following the use of TTPA (1:2000).

Carcinogenesis

In mice, repeated IP administration of THIOTEPA (1.15 or 2.3 mg/kg three times per week for 52 or 43 weeks, respectively) produced a significant increase in the combined incidence of squamous-cell carcinomas of the skin, preputial gland, and ear canal, and combined incidence of lymphoma and lymphocytic leukemia. In other studies in mice, repeated IP administration of THIOTEPA (4 or 8 mg/kg three times per week for 4 weeks followed by a 20-week observation period or 1.8 mg/kg three times per week for 4 weeks followed by a 35-week observation period) resulted in an increased incidence of lung tumors. In rats, repeated IP administration of THIOTEPA (0.7 or 1.4 mg/kg three times per week for 52 or 34 weeks, respectively) produced significant increases in the incidence of squamous-cell carcinomas of the skin or ear canal, combined hematopoietic neoplasms, and uterine adenocarcinomas. THIOTEPA given intravenously (IV) to rats (1 mg/kg once per week for 52 weeks)

produced an increased incidence of malignant tumors (abdominal cavity sarcoma, lymphosarcoma, myelosis, seminoma, fibrosarcoma, salivary gland hemangioendothelioma, mammary sarcoma, pheochromocytoma) and benign tumors.

The lowest reported carcinogenic dose in mice (1.15 mg/kg, 3.68 mg/m^2) is approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area. The lowest reported carcinogenic dose in rats (0.7 mg/kg, 4.9 mg/m^2) is approximately 6-fold less than the maximum recommended human therapeutic dose based on body-surface area.

Mutagenesis

THIOTEPA was mutagenic in *in vitro* assays in *Salmonella typhimurium, E. coli,* Chinese hamster lung and human lymphocytes. Chromosomal aberrations and sister chromatid exchanges were observed *in vitro* with THIOTEPA in bean root tips, human lymphocytes, Chinese hamster lung, and monkey lymphocytes. Mutations were observed with oral THIOTEPA in mouse at doses >2.5 mg/kg (8 mg/m^2). The mouse micronucleus test was positive with IP administration of >1 mg/kg (3.2 mg/m^2). Other positive *in vivo* chromosomal aberration or mutation assays included *Drosophila melanogaster*, Chinese hamster marrow, murine marrow, monkey lymphocyte, and murine germ cell.

Impairment of Fertility

THIOTEPA impaired fertility in male mice at PO or IP doses $0.7mg/kg (2.24 mg/m^2), approximately 12-fold less than the maximum recommended human therapeutic dose based on body-surface area. THIOTEPA (0.5 mg) inhibited implantation in female rats when instilled into the uterine cavity.

THIOTEPA interfered with spermatogenesis in mice at IP doses $0.5 mg/kg (1.6 mg/m^2), approximately 17-fold less than the maximum recommended human therapeutic dose based on body-surface area. THIOTEPA interfered with spermatogenesis in hamsters at an IP dose of 1 mg/kg (4.1 mg/m^2), approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area.

Pregnancy

THIOTEPA can cause fetal harm when administered to a pregnant woman. THIOTEPA given by the IP route was teratogenic in mice at doses $1mg/kg (3.2 mg/m^2), approximately 8-fold less than the maximum recommended human therapeutic dose based on body-surface area. THIOTEPA given by the IP route was teratogenic in rats at doses $3mg/kg (21 mg/m^2), approximately equal to the maximum recommended human therapeutic dose based on body-surface area. THIOTEPA was lethal to rabbit fetuses at a dose of 3 mg/kg (41 mg/m^2), approximately 2 times the maximum recommended human therapeutic dose based on body-surface area. Patients of childbearing potential should be advised to avoid pregnancy. There are no adequate and well-controlled studies in pregnant women. If THIOTEPA is used during pregnancy, or if pregnancy occurs during THIOTEPA therapy, the patient and partner should be apprised of the potential hazard to the fetus.

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