THIOTEPA FOR INJECTION, USP
15 mg/Vial

Label  Single Dose Vial

SIZE  45 x 17 mm
BAR CODE  GS1 Data Bar (Stacked) - (01)00301439565017
FONTS  Helvetica LT Std Condensed Family

USUAL DOSAGE: See package insert.
PROTECT FROM LIGHT AT ALL TIMES.
STORE BETWEEN 2°C TO 8°C (36°F TO 46°F).
15 mg/vial
Rx only

200 %
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 with thiotepa in bean root tips, human lymphocytes, and hamster lung and human lymphocytes. Chromosomal aberrations and sister chromatid exchanges were observed in vivo with thiotepa in bean root tips and human lymphocytes, thiotepa was mutagenic in mouse at doses > 2.5 mg/kg (8 mg/m²), approximately 2-fold less than the maximum recommended human therapeutic dose (4 mg/m²), based on body-surface area. Thiotepa given by the IP route was teratogenic in mice at doses ≥ 1 mg/kg (3.2 mg/m²), 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/m²), approximately two times the maximum recommended human therapeutic dose based on body-surface area. Effective contraception should be used during thiotepa therapy if either the patient or partner is of childbearing potential. There are no adequate and well-controlled studies in pregnant women. 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.

Thiotepa is contraindicated in patients with a known hypersensitivity (allergy) to this preparation. 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. The lowest reported carcinogenic dose in mice (1.15 mg/kg, 3.68 mg/m²) is approximately 2-fold less than the maximum recommended human therapeutic dose (4 mg/m²), based on body-surface area. Other positive carcinogenic effects have been observed with thiotepa in hamster lung and human lymphocytes, thiotepa was mutagenic in mouse at doses > 2.5 mg/kg (8 mg/m²), approximately 2-fold less than the maximum recommended human therapeutic dose (4 mg/m²), based on body-surface area. Thiotepa was lethal to rabbit fetuses at a dose of 3 mg/kg (41 mg/m²), approximately two times the maximum recommended human therapeutic dose based on body-surface area. Effective contraception should be used during thiotepa therapy if either the patient or partner is of childbearing potential. There are no adequate and well-controlled studies in pregnant women. 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.
Patients with papillary carcinoma of the bladder are treated with thiotepa. Thiotepa is a cytotoxic anticancer drug®

Intravenous Administration:

Dosage must be carefully individualized. A slow response to thiotepa does not necessarily indicate a lack of effect. Therefore, increasing the frequency of dosing may only increase 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 not be administered more frequently than weekly in order to preserve correlation between dose and blood counts.

Dosage and Administration

Since absorption from the gastrointestinal tract is variable, thiotepa should not be administered orally. Dosage must be carefully individualized. A slow response to thiotepa does not indicate a lack of effect. Therefore, increasing the frequency of dosing may only increase 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 not be administered more frequently than weekly in order to preserve correlation between dose and blood counts.

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.

Preparation of Solution:

Thiotepa for injection should be reconstituted with 1.5 mL of sterile water for injection resulting in a drug concentration of approximately 10 mg/mL. The actual withdrawable quantities and concentration achieved are illustrated in the following table:

<table>
<thead>
<tr>
<th>Label Claim (mg/vial)</th>
<th>Actual Content (mg/vial)</th>
<th>Amount of Diluent to be Added (mL)</th>
<th>Approximate Withdrawal Volume (mL)</th>
<th>Approximate Withdrawal Amount (mg/vial)</th>
<th>Approximate Withdrawn Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>15</td>
<td>1.5</td>
<td>1.4</td>
<td>1.4</td>
<td>10.4</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>1.5</td>
<td>1.4</td>
<td>1.4</td>
<td>10.4</td>
</tr>
</tbody>
</table>

The reconstituted solution is hypotonic and should be diluted with sodium chloride injection (0.9% sodium chloride) 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 sodium chloride injection should be used immediately.

In order to eliminate haze, filter solutions 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.

+*Polyethylene membrane (Gelman’s Sterile Aerodisc®, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore’s MILLEX®-GS Filter Unit).

Initial 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 as rapid intravenous administration in doses of 0.3 to 0.4 mg/kg. Doses should be given at 1 to 4 week intervals.

Intracavitary Administration: The dosage recommended is 0.6 to 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 mL of Sodium Chloride solution is flushed 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.

Handling and Disposal: Follow safe cytotoxic agent handling procedures. Several guidelines on this subject have been published.15 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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

HOW SUPPLIED

Thiotepa for injection, USP, for single use only, is available in vials containing 15 mg of nonpyrogenic, sterile hypodermized powder, supplied as follows:

NDC 0143-9565-01. Unit container contains 1 x 15 mg single dose vial thiotepa.

Store in a refrigerator between 2° to 8°C (36° to 46°F). PROTECT FROM LIGHT AT ALL TIMES.

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceutical Corp. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

For Product Inquiry call 1-877-845-0689.

REFERENCES


3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.


Manufactured by THYMOORGAN PHARMAZIE GmbH, Schiffgraben 23, 36000 Goslar, Germany.

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