IARC MONOGRAPHS

PHARMACEUTICALS

VOLUME 100 A
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 14-21 October 2008

LYON, FRANCE - 2012

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer
World Health Organization

TREOSULFAN

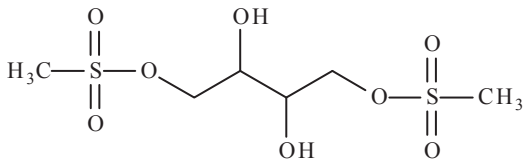
Treosulfan was considered by previous IARC Working Groups in 1980 and 1987 (IARC, 1981, 1987a). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Chem. Abstr. Serv. Reg. No.: 299-75-2
Chem. Abstr. Name: 1,2,3,4-Butanetetrol, 1,4-dimethanesulfonate, (2*S*, 3*S*)-
IUPAC Systematic Name: [(2*S*,3*S*)-2,3-Dihydroxy-4-methylsulfonyloxybutyl]methanesulfonate
Synonyms: 1,2,3,4-Butanetetrol, 1,4-dimethanesulfonate, [*S*-(*R**,*R**)]-; dihydroxybusulfan; dihydroxymyleran; Ovastat; (2*S*,3*S*)-threitol 1,4-bismethanesulfonate; L-threitol 1,4-bis(methanesulfonate)
Description: White, odourless, crystalline powder (IARC, 1981)

1.1.1 Structural and molecular formulae, and relative molecular mass



$C_6H_{14}O_8S_2$
Relative molecular mass: 278.3

1.2 Use of the agent

Treosulfan is a prodrug of a bifunctional alkylating cytotoxic agent (Scheulen *et al.*, 2000; Sweetman, 2008).

1.2.1 Indications

Treosulfan is used to treat ovarian cancer (Royal Pharmaceutical Society of Great Britain, 2007). In addition, preclinical and clinical activity have been demonstrated against some other solid tumours, and haematological malignancies (Scheulen *et al.*, 2000). It has also been used for bone-marrow ablation before stem-cell transplantation, and to treat malignant melanoma, and breast cancer.

1.2.2 Dosage

Treosulfan is given orally or by intravenous or intraperitoneal administration. Treosulfan is available as 1 g and 5 g powders for reconstitution for injection or as a 250 mg capsule (Royal Pharmaceutical Society of Great Britain, 2007).

1.2.3 Trends in use

Treosulfan is commercially available in Europe for the treatment of ovarian cancer. In the USA, treosulfan is under clinical development and, at the time of writing, had not yet received approval from the US Food and Drug Administration (FDA) (Anakena, 2008). In April 2011, the US National Cancer Institute Clinical Trials database listed 15 active clinical trials using treosulfan, alone or in combination, in the treatment regimens (NCI, 2011). Treosulfan is listed in the FDA's orphan drug database (FDA, 2008).

2. Cancer in Humans

The first evaluation of treosulfan as a carcinogen (IARC, 1981) was based on the earlier results of the Danish cohort described below.

Two epidemiological studies have focused on the risk of leukaemia following treatment with treosulfan. In a cohort of 553 Danish patients with ovarian cancer treated only with treosulfan and followed for 9 years (over 1700 person–years) after treatment, 13 patients developed acute myeloid leukaemia, mostly within 5 years after the start of chemotherapy. The relative risk of acute myeloid leukaemia was in excess of 100, and there was a significant correlation between cumulative dose of treosulfan and risk of leukaemia (Pedersen-Bjergaard *et al.*, 1985). In an international case–control study of women treated for ovarian cancer, Kaldor *et al.* (1990) found that the relative risk was 3.6 in the group treated with the lowest dose of treosulfan, and 33.0 within the highest dose group. [The Working Group noted that there may have been an overlap between the two studies, as the case–control study included Denmark, and covered a similar time period as the Danish cohort study.]

3. Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Treosulfan is a prodrug that is converted non-enzymatically first to a mono-epoxide – (2*S*,3*S*)-1,2-epoxy-3,4-butanediol-4-methanesulfonate – and then to a diepoxide – L-diepoxybutane, which is also a metabolite of butadiene – under physiological conditions. Such conversions are assumed to account for the alkylating and therapeutic activities of treosulfan. After oral and intravenous administration of treosulfan to humans, the parent drug is found in the serum at a higher concentration after the intravenous dosing, and about 15% of unchanged drug is excreted in urine (Hilger *et al.*, 2000)

4.2 Genotoxic effects

4.2.1 Interaction with DNA

As a bifunctional alkylating agent, treosulfan alkylates DNA and creates interstrand cross-links in cell-free systems (plasmid DNA), and in intact cells (Hartley *et al.*, 1999), preferentially at guanine residues. Prior to any short-term tests for genotoxicity, treosulfan was predicted to be active based on its structure (Shelby, 1988).

4.2.2 Mutagenicity in vitro

Treosulfan is mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 in the absence of metabolic activation, as is diepoxybutane without external activation (Zeiger & Pagano, 1989). These strains detect base-pair substitutions at G:C base pairs. Treosulfan is

not mutagenic to TA102, which is sensitive to base-pair substitutions at A:T (Abu-Shakra *et al.*, 2000).

Treosulfan is mutagenic in Chinese hamster ovary cells, at the guanine phosphorybosyl transferase *(Gpt)* locus (Zhu & Zeiger, 1993); diepoxybutane is also mutagenic, but at a lower concentration.

4.2.3 Mutagenicity in vivo

Earlier literature contains reports that treosulfan induced chromosomal aberrations in several plant species, including *Allium cepa* (onion), *Hordeum sativum* (barley), *Nigella damascena* (love-in-a-mist), and *Vicia faba* (vetch), but did not produce chlorophyll mutations in *Arabidopsis thaliana* (thale cress) (IARC, 1981, 1987b). Subsequently, in an in-vivo study, treosulfan gave positive results in a mouse bone-marrow micronucleus assay (Shelby *et al.*, 1989), inducing an approximately 20-fold increase in the frequency of micronucleated polychromatic erythrocytes. In another study, treosulfan induced micronuclei in mouse bone-marrow, and peripheral blood cells (Gulati *et al.*, 1990).

4.3 Synthesis

Treosulfan is carcinogenic via a genotoxic mechanism.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of treosulfan. Treosulfan causes acute myeloid leukaemia.

No data were available to the Working Group for the carcinogenicity of treosulfan in experimental animals.

Treosulfan is *carcinogenic to humans (Group 1).*

References

Abu-Shakra A, McQueen ET, Cunningham ML (2000). Rapid analysis of base-pair substitutions induced by mutagenic drugs through their oxygen radical or epoxide derivatives. *Mutat Res*, 470: 11–18. PMID:10986471

Anakena (2008). *Product Information*. Barcelona, Spain. Available at: http://www.treosulfan.com/product_information/ (accessed, April 2011)

FDA (2008). *Excel Orphan Designations spreadsheet*. Available at: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm (accessed, February 2011)

Gulati DK, Wojciechowski JP, Kaur P (1990). Comparison of single-, double- or triple-exposure protocols for the rodent bone marrow/peripheral blood micronucleus assay using 4-aminobiphenyl and treosulphan. *Mutat Res*, 234: 135–139. PMID:2366781

Hartley JA, O'Hare CC, Baumgart J (1999). DNA alkylation and interstrand cross-linking by treosulfan. *Br J Cancer*, 79: 264–266. 1038/sj.bjc.6690043 doi:10.1038/sj.bjc.6690043 PMID:9888467

Hilger RA, Jacek G, Oberhoff C *et al.* (2000). Investigation of bioavailability and pharmacokinetics of treosulfan capsules in patients with relapsed ovarian cancer. *Cancer Chemother Pharmacol*, 45: 483–488. 1007/s002800051023 doi:10.1007/s002800051023 PMID:10854136

IARC (1981). Some antineoplastic and immunosuppressive agents. *IARC Monogr Eval Carcinog Risk Chem Hum*, 26: 1–411. PMID:6944253

IARC (1987a). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203

IARC (1987b). Genetic and related effects: An updating of selected IARC monographs from Volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 6: 1–729. PMID:3504843

Kaldor JM, Day NE, Pettersson F *et al.* (1990). Leukemia following chemotherapy for ovarian cancer. *N Engl J Med*, 322: 1–6. doi:10.1056/NEJM199001043220101 PMID:2104664

NCI (2011). *Search for Clinical Trials: Advanced Search*. Available at: http://www.cancer.gov/clinicaltrials/search (accessed, April 2011)

Pedersen-Bjergaard J, Ersbøll J, Sørensen HM *et al.* (1985). Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphomas. Comparison with results obtained in patients treated for Hodgkin's disease and ovarian carcinoma with other alkylating agents. *Ann Intern Med*, 103: 195–200. PMID:4014901

Royal Pharmaceutical Society of Great Britain (2007). *British National Formulary*, No. 54. London: BMJ Publishing Group Ltd./RPS Publishing.

Scheulen ME, Hilger RA, Oberhoff C *et al.* (2000). Clinical phase I dose escalation and pharmacokinetic study of high-dose chemotherapy with treosulfan and autologous peripheral blood stem cell transplantation in patients with advanced malignancies. *Clin Cancer Res*, 6: 4209–4216. PMID:11106234

Shelby MD (1988). The genetic toxicity of human carcinogens and its implications. *Mutat Res*, 204: 3–15. doi:10.1016/0165-1218(88)90113-9 PMID:3277048

Shelby MD, Gulati DK, Tice RR, Wojciechowski JP (1989). Results of tests for micronuclei and chromosomal aberrations in mouse bone marrow cells with the human carcinogens 4-aminobiphenyl, treosulphan, and melphalan. *Environ Mol Mutagen*, 13: 339–342. doi:10.1002/em.2850130410 PMID:2737185

Sweetman SC, editor (2008). *Martindale: The Complete Drug Reference*. London: Pharmaceutical Press. Available at: http://www.medicinescomplete.com/mc/

Zeiger E & Pagano DA (1989). Mutagenicity of the human carcinogen treosulphan in Salmonella. *Environ Mol Mutagen*, 13: 343–346. doi:10.1002/em.2850130411 PMID:2544419

Zhu S & Zeiger E (1993). Mutagenicity of the human carcinogen treosulphan, and its hydrolysis product, dl-1,2:3,4-diepoxybutane in mammalian cells. *Environ Mol Mutagen*, 21: 95–99. doi:10.1002/em.2850210113 PMID:8419160