Stavudine

2',3'-Didehydro-3'-deoxythymidine

Stavudine is an antiviral drug for the treatment of human immunodeficiency virus (HIV) infection. It is a thymidine nucleoside analog that is a competitive inhibitor of HIV reverse transcriptase and a chain terminator in DNA synthesis. This nucleoside reverse transcriptase inhibitor (NRTI) is available by prescription only.

Stavudine passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

No cancer epidemiology studies were identified.

Animal carcinogenicity data

- Long-term diet studies in mice
  - 24-month studies in male and female CD-1 mice: U.S. FDA (1998)
    - *Increase in liver adenoma, combined liver adenoma and carcinoma (by pairwise comparison and trend), and liver carcinoma (by trend) in males*
    - *Increase in liver adenoma (by trend), liver carcinoma, and combined liver adenoma and carcinoma (by pairwise comparison and trend) in females*

- Long-term diet studies in rats
  - 24-month studies in male and female Sprague-Dawley rats: U.S. FDA (1998, pp. 8, 9, 15)
    - *Increases in liver adenoma, liver cholangioma, cholangiocarcinoma, and urinary bladder transitional cell carcinoma (by pairwise comparison and trend), and hepatocholangiocellular adenoma,thyroid gland follicular adenoma, Zymbal's gland, kidney adenoma, skin sebaceous cell adenoma, and pituitary adenoma (by trend) in males*
    - *Increases in liver adenoma, liver cholangiocarcinoma, liver hemangiosarcomas (by pairwise comparison and trend), and liver cholangioma, and skin and external ear keratoacanthoma (by trend) in females*

Other relevant data

- Genotoxicity
    - As reviewed in U.S. FDA (1993, pp. 28-33)
        - Mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 (*negative*)
        - Mutagenicity in *Escherichia coli* WP2 uvrA (*negative*)
        - Mutagenicity in Chinese hamster ovary/hypoxanthine guanine phosphoribosyl transferase (HGPRT) assay (*negative*)
        - In vitro chromosomal aberration assay in human peripheral blood lymphocytes (*positive)*
        - *In vivo* peripheral blood erythrocyte micronucleus assay in CD-1 mice (*negative*)
        - *In vivo* bone marrow micronucleus assay in CD-1 mice (*positive*)
        - *In vivo* bone marrow micronucleus assay in Sprague-Dawley rats (*negative*)
        - *In vitro* transformation in Balb/c 3T3 fibroblast cells (*positive*)
    - Mutagenicity (HPRT loci) in human TK6 lymphoblastoid cells (*positive*): Carter *et al*. (2007)

- Structure activity considerations
    - Stavudine belongs to the group of nucleoside analogues. Several chemicals in this group are Proposition 65 carcinogens, such as Ganciclovir, Zalcitabine, and Zidovudine (AZT).

References[1]

Carter MM, Torres SM, Cook DL, McCash CL, Yu M, Walker VE, Walker DM (2007). Relative mutagenic potencies of several nucleoside analogs, alone or in drug pairs, at the *HPRT* and *TK* loci of human TK6 lymphoblastic cells. *Env Mol Mut* **48**:239-247.

U.S. Food and Drug Administration (U.S. FDA, 1998). Statistical review and evaluations. *Animal carcinogenicity*. NDA 20-412/SLR-005. Washington D.C.

U.S. Food and Drug Administration (U.S. FDA, 1993). Pharmacology review. *Stavudine*. NDA 20-412. Washington D.C.

[1] Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.