Dacarbazine

CAS No. 4342-03-4

Reasonably anticipated to be a human carcinogen
First listed in the Fourth Annual Report on Carcinogens (1985)

\[
\text{H}_3\text{C}\text{N}\text{N}\text{N}\text{H}_2\text{N}\text{N}\text{N}\text{H}\text{N}\text{N}\text{N}\text{H}_3
\]

Carcinogenicity

Dacarbazine is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dacarbazine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. It caused cancer of the mammary gland (adenocarcinoma), spleen (lymphosarcoma), and thymus (lymphosarcoma) in male and female rats following dietary exposure and in female rats following intraperitoneal injection. It also caused brain tumors (cerebral ependymoma) in female rats following dietary exposure. Tumors occurred as soon as 18 weeks after the start of dietary exposure. In mice, intraperitoneal injection of dacarbazine caused lung tumors in both sexes, lymphoma and blood-vessel tumors (hemangioma in the spleen) in males, and uterine tumors in females (IARC 1981).

Since dacarbazine was listed in the Fourth Annual Report on Carcinogens, an additional study in rodents has been identified. Prenatal exposure to dacarbazine caused tumors in rats, predominantly cancer of the peripheral nerves (malignant neurinoma) (IARC 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to dacarbazine. A retrospective cohort study of Hodgkin disease patients treated with various types of combination chemotherapy or radiotherapy evaluated records from 1,032 consecutive patients from 1965 to 1978. No secondary cases of solid tumors or acute non-lymphoblastic leukemia occurred in the subpopulation of patients treated with dacarbazine plus Adriamycin, Bleomycin, and Vinblastine (ABVD therapy) alone or in combination with radiotherapy; however, the number of patients treated with ABVD therapy was small (Valagussa et al. 1980, 1982, IARC 1981, 1987).

Since dacarbazine was listed in the Fourth Annual Report on Carcinogens, another study of Hodgkin disease patients has been identified, which found no increased risk of acute leukemia among patients treated with ABVD therapy alone or in combination with nonalkylating chemotherapeutic drugs (Brusamolino et al. 1998).

Properties

Dacarbazine is a triazene prodrug with alkylation (methylating) properties. It exists at room temperature as a white to ivory-colored microcrystalline substance. It is slightly soluble in water and is stable in neutral solutions when stored in the dark. However, it decomposes rapidly to 4-diazoimidazole-5-carboxamide when exposed to light, and it decomposes explosively at high temperatures (250°C to 255°C) (IARC 1981). Physical and chemical properties of dacarbazine are listed in the following table.

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>182.2 a</td>
</tr>
<tr>
<td>Melting point</td>
<td>205°C b</td>
</tr>
<tr>
<td>Log $K_{ow}$</td>
<td>0.24 c</td>
</tr>
<tr>
<td>Water solubility</td>
<td>4.22 g/L at 25°C b</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>$2.2 \times 10^{-4}$ mm Hg at 25°C b</td>
</tr>
<tr>
<td>Dissociation constant ($pK_a$)</td>
<td>4.42 b</td>
</tr>
</tbody>
</table>

Sources: aHSDB 2009, bChemIDplus 2009.

Use

Dacarbazine has been used as an antineoplastic agent since the early 1970s, usually in combination regimens. Dacarbazine is used in the treatment of malignant melanoma, Hodgkin disease, neuroblastoma, osteogenic sarcoma, malignant glucagonoma, and soft-tissue sarcoma, such as leiomyosarcoma, fibrosarcoma, and rhabdomyosarcoma. It is occasionally used in therapy for other neoplastic diseases that have become resistant to alternative treatments (IARC 1981, Medline-Plus 2003).

Production

Dacarbazine is not reported to be produced in the United States. In 2009, it was produced by one manufacturer in China and one in Europe (SRI 2009) and was available from one supplier worldwide, in the United States (ChemSources 2009). Volumes of U.S. imports of dacarbazine have not been reported (IARC 1981). In 2009, nine drug products containing dacarbazine as the active ingredient were produced by five manufacturers (FDA 2009).

Exposure

Dacarbazine is available as an injectable solution in 100-, 200-, and 500-mg vials (FDA 2009). The typical initial dose is 2 to 4.5 mg/kg of body weight per day intravenously or intra-arterially for 10 days, repeated every 4 weeks, or 100 to 250 mg/m² of body surface area for 5 days, repeated every 3 weeks (IARC 1981). Health professionals and support staff, such as pharmacists, nurses, physicians, and custodians, may be exposed to dacarbazine by dermal contact, inhalation, or accidental ingestion during drug preparation, or administration or cleanup of medical waste, including excretions of patients treated with dacarbazine (Zimmerman et al. 1981, NIOSH 2004). Workers involved in formulation or packaging of dacarbazine drug products may also be exposed. In humans, about half of the drug is excreted unchanged in the urine (Chabner et al. 2001). The risks from occupational exposure can be avoided through use of appropriate containment equipment and work practices (Zimmerman et al. 1981).

Regulations

Food and Drug Administration (FDA)

Dacarbazine is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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References


