Dacarbazine: Drug information

(For additional information see "Dacarbazine: Patient drug information" and see "Dacarbazine: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Experienced physician:

It is recommended that dacarbazine be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

In treatment of each patient, the physician must weigh carefully the possibility of achieving therapeutic benefit against the risk of toxicity.

Bone marrow suppression:

Hemopoietic depression is the most common toxicity with dacarbazine.

Hepatic effects:

Hepatic necrosis has been reported.

Carcinogenic/teratogenic:

Studies have demonstrated this agent to have a carcinogenic and teratogenic effect when used in animals.

Brand Names: Canada

Dacarbazine for Injection, BP

Pharmacologic Category

Antineoplastic Agent, Alkylating Agent (Triazene)

Dosing: Adult

Note: Dacarbazine is associated with a high emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Roila 2010).

Hodgkin lymphoma: ABVD regimen: IV: 375 mg/m^2 on days 1 and 15 every 4 weeks (in combination with doxorubicin, bleomycin, and vinblastine)

Metastatic malignant melanoma: IV: 250 mg/m^2 over 30 minutes once daily on days 1 to 5 every 3 weeks (Middleton 2000)

Metastatic melanoma (off-label dosing/combinations): IV:

CVD regimen: 800 mg/m^2 over 60 minutes on day 1 every 3 weeks (in combination with cisplatin and vinblastine) (Atkins 2008; Eton 2002)

Biochemotherapy regimen: 800 mg/m^2 over 60 minutes on day 1 every 3 weeks (in combination with cisplatin, vinblastine, interleukin-2 and interferon alfa-2b) (Flaherty 2014) Medullary thyroid cancer, advanced (off-label use): IV: 200 mg/m^2 once daily for 5 days every 6 weeks (in combination with fluorouracil and streptozocin) or 600 mg/m^2 once daily for 2 days every 3 or 4 weeks (in combination with cyclophosphamide and vincristine) or 250 mg/m^2 over 15 to 30 minutes once daily for 5 days every 4 weeks (in combination with fluorouracil) (Orlandi 1994; Schlumberger 1995; Wu 1994). Additional data may be necessary to further define the role of dacarbazine in this condition.

Pancreatic neuroendocrine tumors, advanced (off-label use): IV: 850 mg/m^2 over 60 to 90 minutes on day 1 every 4 weeks (Ramanathan 2001).

Pheochromocytoma, malignant (off-label use): IV: 600 mg/m^2 once daily for 2 days every 3 or 4 weeks (in combination with cyclophosphamide and vincristine) (Huang 2008). Additional data may be necessary to further define the role of dacarbazine in this condition.

Soft tissue sarcoma, advanced (off-label use): MAID regimen: IV: 250 mg/m^2/day as a continuous infusion for 4 days every 3 weeks (total of 1,000 mg/m^2/cycle) (in combination with mesna, doxorubicin, and ifosfamide) (Antman 1993; Antman 1998)

Dosing: Pediatric

(For additional information see "Dacarbazine: Pediatric drug information")

Note: Dacarbazine is associated with a high emetic potential; antiemetics are recommended to prevent nausea and vomiting (Dupuis 2011).

Hodgkin lymphoma: Children and Adolescents: ABVD regimen: IV: 375 mg/m^2 over 30 to 60 minutes on days 1 and 15 every 4 weeks (in combination with doxorubicin, bleomycin, and vinblastine) (Hutchinson 1998)

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

There are no dosage adjustments provided in the manufacturer's labeling. The following adjustments have been recommended (Kintzel 1995):

CrCl 46 to 60 mL/minute: Reduce dose to 80% of usual dose

CrCl 31 to 45 mL/minute: Reduce dose to 75% of usual dose

CrCl ≤30 mL/minute: Reduce dose to 70% of usual dose

Dosing: Hepatic Impairment

There are no dosage adjustments provided in the manufacturer's labeling. May cause hepatotoxicity; monitor closely for signs of toxicity.

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as

for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution Reconstituted, Intravenous:

Generic: 100 mg (1 ea); 200 mg (1 ea)

Solution Reconstituted, Intravenous [preservative free]:

Generic: 200 mg (1 ea)

Generic Equivalent Available (US) Yes

Dosage Forms: Canada Information with regard to form, strength, and availability of products uniquely available in Canada but currently not available in the US. Refer also to Dosage forms.

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution Reconstituted, Intravenous:

Dacarbazine for injection, BP: 600 mg

Administration Dacarbazine is associated with a high emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2010).

Infuse over 15 to 60 minutes; rapid infusion may cause severe venous irritation. Other infusion durations have been reported; refer to literature and/or regimen for infusion details (may vary by protocol).

Dacarbazine is an irritant; local reactions may occur (Perez Fidalgo 2012). Monitor infusion site.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

Use

Hodgkin lymphoma: Treatment of Hodgkin lymphoma (in combination with other chemotherapy agents)

Metastatic malignant melanoma: Treatment of metastatic malignant melanoma

Use: Off-Label

Medullary thyroid cancer (advanced); Pancreatic neuroendocrine tumors (advanced); Pheochromocytoma (malignant); Soft-tissue sarcomas (advanced)

Medication Safety Issues

Sound-alike/look-alike issues:

Dacarbazine may be confused with dactinomycin, procarbazine

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions Frequency not always defined.

Central nervous system: Infusion-site pain

Dermatologic: Alopecia

Gastrointestinal: Nausea and vomiting (>90%), anorexia

Hematologic & oncologic: Bone marrow depression (onset: 5 to 7 days; nadir: 7 to 10 days; recovery: 21 to 28 days), leukopenia, thrombocytopenia

<1%, postmarketing, and/or case reports: Anaphylaxis, anemia, diarrhea, dysgeusia, eosinophilia, erythema, facial flushing, facial paresthesia, flu-like symptoms (fever, myalgia, malaise), hepatic necrosis, increased liver enzymes (transient), paresthesia, renal function test abnormality, skin photosensitivity, skin rash, urticaria, venous obstruction (hepatic vein)

Contraindications

Hypersensitivity to dacarbazine or any component of the formulation

Canadian labeling: Additional contraindications (not in the US labeling): Prior severe myelosuppression

Warnings/Precautions

Concerns related to adverse effects:

• Anaphylaxis: May occur following dacarbazine administration.

• Bone marrow suppression: **[US Boxed Warning]: Bone marrow suppression is the most common toxicity;** leukopenia and thrombocytopenia may be severe; may result in treatment delays

or discontinuation; anemia may also occur. Monitor CBC with differential. The onset for leukopenia is ~14 days (range: 10 to 30 days) and the duration is ~1 to 3 weeks. The onset for thrombocytopenia is ~18 days (range: 12 to 30 days) and the duration is ~1 to 3 weeks.

• Carcinogenic/teratogenic: **[US Boxed Warning]: Studies have demonstrated this agent to be carcinogenic and/or teratogenic when used in animals.**

• Extravasation: Dacarbazine is an irritant; local reactions may occur (Perez Fidalgo 2012). According to the manufacturer, extravasation may result in tissue damage and severe pain.

• Gastrointestinal toxicity: Dacarbazine is associated with a high emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2010).

• Hepatic effects: **[US Boxed Warning]: Hepatic necrosis has been reported.** Hepatotoxicity may be accompanied with hepatic vein thrombosis and hepatocellular necrosis; may be fatal. Hepatotoxicity usually occurs with combination chemotherapy, but may occur with dacarbazine alone.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment; half-life is increased, monitor for toxicity and consider dosage reduction.

• Renal impairment: Use with caution in patients with renal impairment; half-life is increased, monitor for toxicity and consider dosage reduction.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Other warnings/precautions:

• Experienced physician: **[US Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.** Carefully evaluate the potential benefits of therapy against the risk for toxicity. Adequate laboratory facilities should be available for appropriate monitoring.

Metabolism/Transport Effects

Substrate of CYP1A2 (major), CYP2E1 (major); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Abiraterone Acetate: May increase the serum concentration of CYP1A2 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical).

Risk X: Avoid combination

Cannabis: May decrease the serum concentration of CYP1A2 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates (High risk with Inhibitors). *Risk D: Consider therapy modification*

CYP2E1 Inhibitors (Moderate): May decrease the metabolism of CYP2E1 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

CYP2E1 Inhibitors (Strong): May decrease the metabolism of CYP2E1 Substrates (High risk with Inhibitors). *Risk D: Consider therapy modification*

Cyproterone: May decrease the serum concentration of CYP1A2 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Cyproterone: May decrease the serum concentration of CYP2E1 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Deferasirox: May increase the serum concentration of CYP1A2 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. Management: Avoid the use of lenograstim 24 hours before until 24 hours after the completion of myelosuppressive cytotoxic chemotherapy. *Risk D: Consider therapy modification*

Lipegfilgrastim: Antineoplastic Agents may diminish the therapeutic effect of Lipegfilgrastim. Management: Avoid concomitant use of lipegfilgrastim and myelosuppressive cytotoxic chemotherapy. Lipegfilgrastim should be administered at least 24 hours after the completion of myelosuppressive cytotoxic chemotherapy. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Obeticholic Acid: May increase the serum concentration of CYP1A2 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Peginterferon Alfa-2b: May increase the serum concentration of CYP1A2 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

SORAfenib: May decrease the serum concentration of Dacarbazine. Sorafenib may also increase the concentration of dacarbazine's active metabolite. *Risk C: Monitor therapy*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Teriflunomide: May decrease the serum concentration of CYP1A2 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease

modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Vemurafenib: May increase the serum concentration of CYP1A2 Substrates (High risk with Inhibitors). Management: Consider alternatives to such combinations whenever possible, particularly if the CYP1A2 substrate has a relatively narrow therapeutic index. *Risk D: Consider therapy modification*

Pregnancy Risk Factor

C (show table)

Pregnancy Implications

[US Boxed Warning]: Studies have demonstrated this agent to be carcinogenic and/or teratogenic when used in animals; adverse effects have been observed in animal reproduction studies. Women of reproductive potential should avoid becoming pregnant during treatment. The European Society for Medical Oncology has published guidelines for diagnosis, treatment, and follow-up of cancer during pregnancy. The guidelines recommend referral to a facility with expertise in cancer during pregnancy and encourage a multidisciplinary team (obstetrician, neonatologist, oncology team). In general, if chemotherapy is indicated, it should be avoided during in the first trimester, there should be a 3-week time period between the last chemotherapy dose and anticipated delivery, and chemotherapy should not be administered beyond week 33 of gestation (Peccatori 2013). An international consensus panel has published guidelines for hematologic malignancies during pregnancy. Dacarbazine is a component of the ABVD regimen, which is used for the treatment of Hodgkin lymphoma. If treatment cannot be deferred until after delivery in patients with early stage Hodgkin lymphoma, ABVD may be administered safely and effectively in the latter phase of pregnancy (based on limited data); for patients with advanced-stage disease, ABVD can be administered in the second and third trimesters (Lishner 2016).

Breast-Feeding Considerations

It is not known if dacarbazine is excreted in breast milk. Due to the potential for serious adverse reactions in the breast-feeding infant, a decision should be made to discontinue dacarbazine or to discontinue breast-feeding, taking into account the benefits of treatment to the mother.

Monitoring Parameters

CBC with differential, liver function

Mechanism of Action

Alkylating agent which is converted to the active alkylating metabolite MTIC [(methyl-triazene-1-yl)-imidazole-4-carboxamide] via the cytochrome P450 system. The cytotoxic effects of MTIC are manifested through alkylation (methylation) of DNA at the O^6, N^7 guanine positions which lead to DNA double strand breaks and apoptosis. Dacarbazine is non-cell cycle specific (Marchesi 2007).

Pharmacodynamics/Kinetics

Distribution: Exceeds total body water; suggesting binding to some tissue (probably liver) (Perry 2012)

Metabolism: Extensively hepatic to the active metabolite MTIC [(methyl-triazene-1-yl)-imidazole-4-carboxamide]

Half-life elimination: Biphasic: Initial: 19 minutes, Terminal: 5 hours

Excretion: Urine (~40%; as unchanged drug)

Pricing: US

Solution (reconstituted) (Dacarbazine Intravenous)

100 mg (1): $11.34

200 mg (1): $39.42

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

Brand Names: International

Acocard (MX); Arzi (LK); Arzi-100 (PH); Arzi-200 (PH); Bazipar (LK); D.T.I.C. (DE); D.T.I.C.-Dome (AT, SE, ZA); Dabaz (IN, PE); DAC (KR, SG); Dacarb (BR); Dacarbazin (BG, CZ, HU, SI); Dacarbazina (ES); Dacarbazine (NZ); Dacarbazine DBL (MY); Dacarbazine Dome (DK); Dacarbazine For Injection (AU); Dacarzin (PY); Dacatic (FI); Dacimed (LK); Dacin (CH); Dakarbazyn (UA); Decarb (IN, LK); Deticene (AR, CL, CZ, EG, FR, GR, HR, IL, IT, KR, KW, NL, PL, PT, QA, RU, SA, TR, UY, VN); Deticine (HU); Detilem (MX); Detimedac (DE); DTI (HK, KR); DTIC (AT, ZA); DTIC-Dome (BE, GB, KR); Duticin (PH, PK); Oncocarbil (AR, PY); Tiferomed (CR, DO, GT, HN, MX, NI, PA, SV)

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