Drug Monograph

A - Drug Name

procarbazine

COMMON TRADE NAME(S): Matulane®

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B - Mechanism of Action and Pharmacokinetics

Procarbazine was discovered in the late 1950's during a search for monoamine oxidase (MAO) inhibitors with less serious side effects. As early as 1962, clinical trials were reported describing procarbazine's effectiveness in Hodgkin's disease. Procarbazine is an unique antineoplastic agent with multiple sites of action. It inhibits incorporation of small DNA precursors, as well as RNA and protein synthesis. Procarbazine can also directly damage DNA through an alkylation reaction. Procarbazine is not cross-resistant with other alkylating agents. Cell cycle phase-specific (S-phase).

Absorption	Oral: Rapid and complete. Peak plasma levels reached in 60 minutes	
Distribution	Highest levels in liver, kidney, intestinal wall and skin.	
	Cross blood brain barrier?	Yes, rapid equilibration
	PPB	no information found
Metabolism	By kidneys and liver (CYP450)	
	Active metabolites	yes
	Inactive metabolites	yes
Elimination	Predominantly in urine as N-isopropyl-terephthalamic acid	
	Half-life	1 hour

Urine	70% within 24 hours (as metabolites)

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C - Indications and Status

Health Canada Approvals:

- Hodgkin's lymphoma (Stage III and IV)

Other Uses:

- Non-Hodgkin's lymphoma
- Gliomas

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D - Adverse Effects

Emetogenic Potential: High – Consider prophylaxis daily

Extravasation Potential: Not applicable

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Flushing	E
	Hypertension (rare)	E
	Hypotension (rare)	E
	Pericarditis	E
	Tachycardia (rare)	I
	Thromboembolism	E
Dermatological	Alopecia (rare)	E
	Photosensitivity (rare)	E
	Pruritus	E
	Radiation recall reaction	I
	Rash (may be severe)	E
	Skin hyperpigmentation (rare)	E D

	Urticaria (may be severe)	E
Gastrointestinal	Abdominal pain	E
	Anorexia	E
	Ascites (rare)	E
	Constipation	E
	Diarrhea	E
	Dysphagia	E
	GI hemorrhage (or melena)	E
	Mucositis (mild)	E
	Nausea (<50%)	I
	Vomiting (<50%)	I
General	Edema	E
	Fatigue	E
	Flu-like symptoms (myalgia, arthralgia, chills, fever)	I
	Pain	E
Hematological	Eosinophilia	E
	Hemolysis	E
	Hemorrhage	E
	Myelosuppression (common)	E
Hepatobiliary	Jaundice (rare)	E
	↑ LFTs	E
	Pancreatitis	E
Hypersensitivity	Anaphylaxis (rare)	I
	Serum sickness (rare)	I
Infection	Infection	E
Neoplastic	Leukemia (secondary) (2-15%)	L
	MDS (2-15%)	L
	Secondary malignancy (NSCLC)	L
Nervous System	Ataxia	E
	Depressed level of consciousness	E D
	Dizziness	E D
	Hallucinations (10-30%)	E
	Headache	E

	Insomnia (10-30%)	E
	Nystagmus	E
	Other (nightmares - 10-30%)	E
	Peripheral neuropathy (10-20%)	E
	Seizure (rare)	E
	Somnolence	E D
	Syncope (rare)	E
Ophthalmic	Eye disorders (diplopia - rare)	E
	Papilledema	E
	Photophobia	E
Renal	Nephritis	E
Reproductive and breast disorders	Azoospermia (>10%)	E D
	Gynecomastia	D L
	Infertility	D L
	Irregular menstruation (amenorrhea: >10%)	E D
Respiratory	Cough	E
	Dysphonia	E
	Epistaxis	E
	Hemoptysis	E
	Lung infiltrate (<1%)	D
	Pleural effusion	E
	Pulmonary fibrosis (<1%)	D
Urinary	Hematuria	E
	Urinary frequency	E
Vascular	Peripheral ischemia (Raynaud-like syndrome)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common adverse effects of procarbazine are **nausea**, **vomiting** and **myelosuppression**.

Hypersensitivity pneumonitis can occur within hours of ingesting procarbazine and is

characterized by fever, non-productive cough and dyspnea. On chest radiographs, bilateral interstitial infiltrates and pleural effusion can be observed. Patients usually recover following discontinuation of procarbazine. May also consider corticosteroid treatment.

Procarbazine is a weak monoamine oxidase inhibitor that crosses the blood-brain barrier rapidly. ***Neurotoxic effects*** may take the form of altered levels of consciousness, peripheral neuropathy, ataxia or effects of MAO inhibition. Particularly distressing to the patient are frequent nightmares, depression, insomnia, nervousness and hallucinations which occur in 10-30% of patients. ***Peripheral neuropathy*** has been reported in 10-20% of patients and consists of paresthesias in hands and feet, decreased deep tendon reflexes and myalgia.

Bleeding tendencies (petechiae, nosebleeds, vomiting of blood) occur frequently.

Procarbazine has the potential to enhance radiation injury to tissues. While often called ***radiation recall reactions***, the timing of the radiation may be before, concurrent with or even after the administration of procarbazine. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

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E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Use estimated lean weight if obese or ascites present. Patients must have recovered from effects of prior therapy, including radiation; a minimum of 1 month lapse between the end of previous chemotherapy and/or radiation and the initiation of procarbazine is recommended

Adults:

Round dose to the nearest 50 mg. Total daily dose may be taken orally at a single time or in divided fractions throughout the day.

Single-agent (Hodgkin's):

- 2-4 mg/kg daily for the first week, then 4-6 mg/kg daily until maximum response or myelosuppression occurs (See Dosage in Myelosuppression)
- Maintenance: 1-2 mg/kg daily

In combination:
Refer to individual chemotherapy regimen for specific details.
q3w: 100 mg/m^2/day p.o x 2 days
q4w: 100 mg/m^2/day p.o x 14 days (MOPP regimen)

q6w: 60 mg/m^2/day p.o x 14 days (PCV regimen)

Dosage with Toxicity:

Dosage in myelosuppression:

- Modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Hematologic and Non-Hematologic Toxicities."
- Procarbazine should be held if myelosuppression develops (i.e. platelets < 100 x 10^9/L or leukocytes < 4 x 10^9/L); restart after recovery with a reduced dose.

Dosage with toxicity (GI/CNS):

- Hold with neurotoxicity, stomatitis, diarrhea, or bleeding; may restart at a reduced dose after recovery. Discontinue if hypersensitivity or pneumonitis.

Dosage with Hepatic Impairment:

Toxicity increased. Exercise caution and monitor patient closely; decrease dose by 25% for elevated liver function tests (> 1.5 – 5 x ULN). Hold treatment if serum bilirubin > 1.5 X ULN or liver transaminases > 5 X ULN, until recovery occurs.

Dosage with Renal Impairment:

Toxicity increased; monitor patient closely. If creatinine > 1.5 X ULN or BUN > 14.3 mmol/L, the dose should be decreased; no details found.

Children:

Safety and effectiveness have not been established. Tremors, coma, and convulsions have occurred in a few cases.

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F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- **DO NOT** drink alcoholic beverages while taking procarbazine, or for 10-14 days after taking the last capsule(s).
- Follow diet restrictions to avoid food or drinks containing tyramine, caffeine and alcohol while taking procarbazine. Consult a dietician.

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G - Special Precautions

Other:

Procarbazine is **contraindicated** in patients with known hypersensitivity to the drug or inadequate marrow reserve. Ethyl alcohol should not be used since there may be a disulfiram-like reaction. Procarbazine exhibits some MAO inhibitory activity; therefore, sympathomimetic drugs, tricyclic antidepressant drugs (e.g., amitriptyline HCl, imipramine HCl), dietary supplements (e.g. ginseng), and other drugs and food with known high tyramine content, such as aged cheese and ripe bananas, should be avoided. Agents which are CNS depressants should also be avoided. There is an increased risk of second malignancies including NSCLC; patients should be advised to discontinue smoking.

Procarbazine may be responsible for the **infertility** seen in males treated with MOPP (mechlorethamine, Oncovin®, procarbazine, prednisone) for Hodgkin's disease. Procarbazine can cause **azoospermia**, which is often irreversible; and **amenorrhea** in females. Procarbazine is **teratogenic, carcinogenic**, **mutagenic and fetotoxic** and should not be used in **pregnancy**. **Breast feeding** is not recommended due to the potential secretion into breast milk.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Sympathomimetic agents, tricyclic antidepressants, tyramine-rich foods, ginseng, levodopa, MOA and COMT inhibitors	Headache, flushed face, palpitations, rise in blood pressure	Procarbazine is a weak MAO inhibitor	Avoid these drugs and foods during procarbazine therapy (See "Procarbazine Diet" patient information sheet)
Alcohol	Disulfiram-like reaction	Unknown	Avoid alcohol
CNS depressants	Potentiation of CNS depression	Additive	Caution
Digoxin	↓ digoxin effect	Procarbazine interferes with the absorption of digoxin	Monitor blood levels and adjust dose
Antidiabetic agents	↑ hypoglycemia	↓ response to hypoglycemia	Caution
Methotrexate	↑ renal toxicity	Unknown	Use >/= 72 hours apart
Anticonvulsants (i.e. carbamazepine, phenytoin, phenobarbital)	↑ risk of hypersensitivity reactions to procarbazine	May induce procarbazine oxidation to a reactive metabolite that can cause hypersensitivity	Avoid concomitant use; use non-enzyme inducing anticonvulsants
Drugs which should not be used with MAOI	↑ toxicity of these agents		Avoid concomitant use

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and regular
Clinical toxicity assessment (including pulmonary, infection, bleeding, stomatitis, diarrhea, CNS, skin, neurotoxicity)	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Renal function tests	Baseline and regular
Liver function tests	Baseline and regular

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- procarbazine ()

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K - References

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L - Disclaimer

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