DRUG NAME: Procarbazine

SYNONYM(S):

COMMON TRADE NAME(S): MATULANE®

CLASSIFICATION: alkylating agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Procarbazine is a cell cycle phase-nonspecific[1] pro-drug and derivative of hydrazine whose mechanism of action has not yet been clearly defined. Procarbazine may act by inhibiting protein, RNA, and DNA synthesis,[2-4] and by causing free-radical damage to DNA and inhibition of mitosis.[3,5] Procarbazine also has monoamine oxidase (MAO) inhibiting properties[2,3] and is an immunosuppressive agent.[2] Cross resistance with other chemotherapy agents has not been demonstrated.[2]

PHARMACOKINETICS:

Oral Absorption	rapid and complete; peak plasma concentration in 1 h	
Distribution	rapid distribution including into liver, kidneys, intestinal wall, and skin[3]	
	cross blood brain barrier?	yes
	volume of distribution	no information found
	plasma protein binding	no information found
Metabolism	complex spontaneous chemical decomposition and biotransformation to active metabolites,[3,6] primarily in the liver[3] via cytochrome P450 oxidoreductase and mitochondrial monoamine oxidase[7]	
	active metabolite(s)[3,5,6,8]	yes; including azo-and methylazoxy-metabolites and hydrogen peroxide
	inactive metabolite(s)[2,9]	yes; including N-isopropyl-terephthalmamic acid
Excretion	primarily hepatic with some renal[2,3] and pulmonary[10] elimination	
	urine[2-4]	25-70% in 24 h primarily as N-isopropyl-terephthalmamic acid; <5-20% unchanged
	feces[7]	minimal
	terminal half life[3,4]	~1 h; longer for azo-metabolite[8]
	clearance[8]	35.8 L/min

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
Brain tumour[3,4,11,12]
*Lymphoma, Hodgkin's

Other uses:
Lymphoma, non-Hodgkin's[3,4]
Lung cancer[4]
Melanoma[4]
Multiple myeloma[4,9]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to procarbazine or other components of the product[2]
- inadequate marrow reserve as demonstrated by bone marrow aspiration; consideration of this should be given to each patient who has leukopenia, thrombocytopenia, or anemia[2]

Caution:
- to minimize **CNS depression** barbiturates, antihistamines, opiod analgesicss, hypotensive agents, phenothiazines, MAO inhibitors, or catechol-O-methyltransferase inhibitors should be used with caution[13]
- **alcohol** should not be consumed with procarbazine as a disulfiram-like reaction may occur[2] (5-30% incidence)[1,14]
- as procarbazine exhibits some **MAO inhibitory activity**, sympathomimetic drugs (including those in nose drops and cold preparations like pseudoephedrine[3]), local anesthetics[3], tricyclic antidepressants (e.g. amitriptyline, imipramine), and other drugs, dietary supplements (e.g., ginseng) and foods known to react with MAO inhibitors due to high-tyramine content or other physiologic properties should be avoided[13]; see handout **For the Patient: Procarbazine** for further details
- in patients with prexisiting **renal, hepatic, and bone marrow impairment**, severe toxicity may occur[3]; assess hepatic and renal function prior to therapy[2]

Discontinue treatment if any of the following occur[2]:
- central nervous system signs or symptoms such as paresthesias, neuropathies, or confusion
- leukopenia (white blood count <4 x 10^9/L)
- thrombocytopenia (platelets count <100 X 10^9/L)
- hypersensitivity reaction
- stomatitis; including the first small ulceration or persistent spot soreness around the oral cavity
- diarrhea
- hemorrhage or bleeding tendencies

Treatment may be resumed when side effects have resolved; dosage adjustment is recommended.[2]

If radiation or chemotherapy known to have marrow-depressant activity have been used, an interval of one month or longer is recommended by the manufacturer before starting treatment with procarbazine; the length of this interval may also be determined by evidence of bone marrow recovery based on successive bone marrow studies.[2]

Carcinogenicity: Procarbazine is carcinogenic.[2] Instances of new nonlymphoid malignancy, including lung cancer and acute myelocytic leukemia, have been reported with procarbazine in combination with other chemotherapy and/or radiation. The risk of secondary lung cancer from procarbazine appears to be multiplied by tobacco use.

Mutagenicity: Mutagenic in bacterial and mammalian test systems.[2,3]

Fertility: Procarbazine may cause acute ovarian failure, acute amenorrhea, and menopause.[2] Azoospermia and sterility have occurred in combination with other chemotherapeutic agents; the extent of procarbazine involvement in male germ-cell damage is unknown.[2]

Pregnancy: FDA Pregnancy Category D.[4] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[15]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic reactions; including rash
auditory/hearing	hearing loss
blood/bone marrow/ febrile neutropenia	anemia; hemolytic anemia; hemolysis; anisocytosis[3]; poikilocytosis[3]; Heinz-Ehrlich inclusion bodies in erythrocytes
	bone marrow suppression; typically occurs 2-8 weeks after the start of treatment; nadir 3-4 weeks with recovery by 4-6 weeks[5,9,10]; pancytopenia
	leukopenia; eosinophilia; lymphocytosis
	thrombocytopenia
cardiovascular (arrhythmia)	tachycardia
cardiovascular (general)	angina
	cardiotoxicity
	hypertension; secondary to MAO inhibition[9]
	hypotension
	pericarditis
constitutional symptoms	chills
	diaphoresis
	fatigue
	fever
	insomnia
dermatology/skin	alopecia
	dermatitis
	flushing
	hyperpigmentation
	photosensitivity
	pruritus
	rash (>10%)[15]; delayed hypersensitivity,[15] typically occurs with the second cycle[15]
	toxic epidermal necrolysis
	urticaria
gastrointestinal	*emetogenic potential: high-moderate*[16]; dose-dependent[15,17]; at doses of 100 mg/m^2 emetogenic potential: low to moderate[15,17]
	anorexia
	ascites

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	constipation
	diarrhea
	dysphagia
	nausea and vomiting (≤90%)[4,15,17,18]; may be severe[3]; may be minimized by increasing the dose over several days[4]; tolerance may commonly occur within a few days[1,9,10,15]
	stomatitis
	xerostomia
hemorrhage	bleeding tendancies: epistaxis, hematemesis, hematuria, hemoptysis, melena, petechiae, purpura, retinal hemorrhage
hepatobiliary/pancreas	hepatic dysfunction
	pancreatitis
infection	immunosuppression; infection including pneumonia, *herpes*, infection
lymphatics	edema
musculoskeletal	weakness
	osteonecrosis
neurology	neurological toxicity; related to MAO inhibition; including: ataxia, coma, convulsions, neuropathy, paresthesia, nystagmus, diminished reflexes, syncope, tremors, dizziness, drowsiness, unsteadiness, fainting, hallucinations, depression, nervousness, apprehension, disorientation,[3] confusion, nightmares, slurred speech; nightmares, nervousness, and hallucinations (≤30%)[9]
ocular/visual	diplopia
	inability to focus
	papilledema
	photophobia
pain	abdominal pain
	headache
	myalgia and arthralgia
pulmonary	cough
	hoarseness
	pulmonary toxicity (<1%)[4]; including pleural effusion and pneumonitis
renal/genitourinary	nephritis
	urinary frequency; nocturia
secondary malignancy	***secondary malignancies (<1-15%)***[4,15]; including lung cancer, acute myelocytic leukemia, and malignant myelosclerosis; the risk of secondary lung cancer appears to be increased by tobacco use; reported in combination with other chemotherapy and/or radiation
sexual/reproductive function	***acute ovarian failure; acute amenorrhea; menopause***
	azoospermia and sterility; reported in combination with other chemotherapeutic agents

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	gynecomastia; reported in prepubertal and early pubertal boys
syndromes	Raynaud-like syndrome
vascular	thrombosis including pulmonary, deep vein, and mesenteric

Adapted from standard reference[2] unless specified otherwise.

Common side effects include dose-limiting severe leukopenia and thrombocytopenia.[1] Nausea and vomiting[2,10] and neurological effects such as headache, nervousness, and insomnia may also commonly occur.[6,7,10]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
alcohol[13,14]	rapid, minor, suspected, disulfiram-like reaction; facial flushing, headache; (5-30% incidence[1,14])	unknown	avoid alcohol for the duration of treatment[14,19] and for 1 week after stopping treatment[19]
sympathomimetic drugs, local anesthetics, tricyclic antidepressants, and other drugs, dietary supplements (e.g., ginseng) and foods known to react with MAO inhibitors due to high-tyramine content or other physiologic properties[2,3,13,14]	headache, flushing, palpitations, nausea and vomiting, or hypertension[13]; flushing has been reported but clinically significant increases in blood pressure have not occurred with the consumption of high-tyramine-containing foods[14]	procarbazine is a weak MAO inhibitor; theoretical inhibition of tyramine metabolism	avoid concurrent use for the duration of treatment and for 1 week after stopping treatment[19] ; routine monitoring of blood pressure; limited evidence regarding the clinical significance of consuming tyramine-containing foods; however, it is generally advised to avoid consumption of these foods[2,14]
anticonvulsants that induce CYP 3A (e.g., carbamazepine, phenytoin, phenobarbital)[20]	induction of CYP 3A may result in the production of a reactive metabolite responsible for hypersensitivity reactions[20]	increased risk of procarbazine hypersensitivity	monitoring for hypersensitivity reactions may be needed
digoxin[13,21]	decreased effect of digoxin	chemotherapy-induced changes to intestinal mucosa[21] may cause a decrease in digoxin absorption[13]	monitor for decreased effect of digoxin; consider monitoring digoxin levels, adjust digoxin dose as needed[21]
methotrexate[14]	delayed, major, possible, increased methotrexate nephrotoxicity	unknown	allow $\geq$72 h between the final dose of procarbazine and initiation of methotrexate

Since procarbazine exhibits some MAO inhibitory activity, it may theoretically interact with drugs that are normally affected by MAOI, including insulin and sulphonylureas (increased hypoglycemic response),[13,22,23] carbamazepine (hypertensive urgency, hyperpyrexia, seizures)[14] and levodopa (hypertension).[24] Careful monitoring may be needed if concurrent use cannot be avoided.

SUPPLY AND STORAGE:

Tablets: sigma-tau Pharmaceuticals Inc. supplies procarbazine as a 50 mg capsule. Store at room temperature and protect from light.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Oral:	Cycle Length: 4-6 weeks[2,11,12,25,26]:	***100 mg/m^2 (range 60-100 mg/m^2) PO once daily for 14 consecutive days (range 7-14 days) starting on day 1 or 2*** (total dose per cycle 1400 mg/m^2 [range 700-1400 mg/m^2]) • round dose to the nearest 50 mg • dose may be given as a single daily dose or in 2-3 divided doses[4]
	n/a[4]:	initial: 2-4 mg/kg PO once daily for 7 consecutive days then increase dose to 4-6 mg/kg PO once daily until response is obtained or leukocyte count <4 x 10^9/L or the platelet count <100 x 10^9/L maintenance: 1-2 mg/kg/day PO • dose may be given as a single daily dose or in 2-3 divided doses
Concurrent radiation:	has been used[15]; no details found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	use with caution; dose modification may be required[13]	
Dosage in hepatic failure:	use with caution; dose modification may be required[13] Approved dosing adjustment guidelines are not available, however the following modifications have been used: • hold if AST/GGT >5 x ULN or bilirubin >25 umol/L until liver function returns to normal[27,28] • hold if bilirubin >85 micromol/L and/or ALT or AST >180[29] • hold if bilirubin >5 mg/dL (>85 micromol/L) and aminotransferases >3xULN; decrease dose by 25% for aminotransferases 1.6-6xULN; use clinical judgement for aminotransferases >6xULN[30]	
Dosage in dialysis:	no information found	

Children:

Oral:

Cycle Length:
undue toxicity e.g., tremors, coma, and seizures have occurred[2,3]; dosage should be individualized with careful monitoring[2,5]

4 weeks[5]:	50-100 mg/m^2 PO once daily for 10-14 consecutive days starting on day 1 (total dose per cycle 500-1400 mg/m^2)
2-4 weeks[5]:	75 mg/m^2 PO for one dose on day 1 (total dose per cycle 75 mg/m^2)

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