After intravenous injection, the plasma half-life of procarbazine is approximately 10 minutes. Approximately 70% of the radioactivity is excreted in the urine as \( N \)-isopropylpyrrolophenalimic acid within 24 hours following both oral and intravenous administration of \( ^{14} \)C-labeled procarbazine.

Procarbazine crosses the blood-brain barrier and rapidly equilibrates between plasma and cerebrospinal fluid after oral administration.

INDICATIONS AND USAGE
Matulane is indicated for use in combination with other anticancer drugs for the treatment of Stage III and IV Hodgkin's disease. Matulane is used as part of the MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) regimen.

CONTRAINDICATIONS
Matulane is contraindicated in patients with known hypersensitivity to the drug or inadequate marrow reserve as demonstrated by bone marrow aspiration. Due consideration of this possible state should be given to each patient who has leukemia, thrombocytopenia or anemia.

WARNINGS
To minimize CNS depression and possible potentiation, barbiturates, antihistamines, narcotics, hypotensive agents or phenothiazines should be used with caution. Ethyl alcohol should not be used since there may be an Antabuse (disulfiram)-like reaction. Because Matulane inhibits some monooxygen oxidase inhibitory activity, sympathomimetic drugs, tricyclic antidepressant drugs (eg, amitriptyline HCI, imipramine HCl) and other drugs and foods with known high tyramine content, such as wine, yogurt, ripe cheese and bananas, should be avoided. A further phenomenon of toxicity common to many hydrazine derivatives is hemolysis and the appearance of Heinz-Ehrlich inclusion bodies in erythrocytes.

Pregnancy
Teratogenic Effects
Pregnancy Category D. Procarbazine hydrochloride can cause fetal harm when administered to a pregnant woman. While there are no adequate and well-controlled studies with procarbazine hydrochloride in pregnant women, there are case reports of malformations in the offspring of women who were exposed to procarbazine hydrochloride in combination with other antineoplastic agents during pregnancy. Matulane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Procarbazine hydrochloride is teratogenic in the rat when given at doses approximately 4 to 13 times the maximum recommended human therapeutic dose of 6 mg/kg/day.

Nonteratogenic Effects
Procarbazine hydrochloride has not been adequately studied in animals for its effects on peri- and postnatal development. However, neonenic tumors were noted in the offspring of rats given intravenous injections of 125 mg/kg of procarbazine hydrochloride on day 22 of gestation. Compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and postnatal development.

Carcinogenesis, Mutagenesis and Impairment of Fertility
Carcinogenesis
The carcinogenicity of procarbazine hydrochloride in mice, rats and monkeys has been reported in a considerable number of studies. Instances of a second nonlymphoid malignancy, including lung cancer and acute myelocytic leukemia, have been reported in patients with Hodgkin's disease treated with procarbazine in combination with other chemotherapy and/or radiation. The risks of secondary lung cancer from treatment appear to be multiplied by tobacco use. The International Agency for Research on Cancer (IARC) considers that there is "sufficient evidence" for the human carcinogenicity of procarbazine hydrochloride when it is given in intensive regimens which include other antineoplastic agents but that there is inadequate evidence of carcinogenicity in humans given procarbazine hydrochloride alone.

Mutagenesis
Procarbazine hydrochloride has been shown to be mutagenic in a variety of bacterial and mammalian test systems.

Impairment of Fertility
Azospermia and antifertility effects associated with procarbazine hydrochloride administration in combination with other chemotherapeutic agents for treating Hodgkin's disease have been reported in human clinical studies. Since these patients received multikcombination therapy, it is difficult to determine to what extent procarbazine hydrochloride alone was involved in the male germ cell damage. The usual Segment I fertility/reproduction studies in laboratory animals have not been carried out with procarbazine hydrochloride. However, compounds which inhibit DNA, RNA and/or protein synthesis might be expected to have adverse effects on gametogenesis.

Unscheduled DNA synthesis in the testis of rabbits and decreased fertility in male mice treated with procarbazine hydrochloride have been reported.

PRECAUTIONS
General
Urgent toxicity may occur if Matulane is used in patients with impairment of renal and/or hepatic function. When appropriate, hospitalization for the initial course of treatment should be considered.

If radiation or a chemotherapeutic agent known to have marrow-depressant activity has been used, an interval of one month or longer without such therapy is recommended before starting treatment with Matulane. The length of this interval may also be determined by evidence of bone marrow recovery based on successive bone marrow studies.

Prompt cessation of therapy is recommended if any one of the following occurs:

- Central nervous system signs or symptoms such as paresthesias, neuraphagies or confusion.
- Leukopenia (white blood count under 4000).
- Thrombocytopenia (platelets under 100,000).
- Hypersensitivity reaction.
- Stomatitis - The first small ulceration or persistent open soreness around the oral cavity is a signal for cessation of therapy.
- Diarrhea - Frequent bowel movements or watery stools.
- Hemorrhage or bleeding tendencies.

Bone marrow depression often occurs 2 to 8 weeks after the start of therapy. If leukopenia occurs, hospitalization of the patient may be needed for appropriate treatment to prevent systemic infection.

Information for Patients
Patients should be warned not to drink alcoholic beverages while on Matulane therapy since there may be an Antabuse (disulfiram)-like reaction. They should also be cautioned to avoid foods with known high tyramine content such as wine, yogurt, ripe cheese and bananas. Over-the-counter drug preparations which contain antihistamines or sympathomimetic drugs should also be avoided. Patients taking Matulane should also be...
warned against the use of prescription drugs without the knowledge and consent of their physician. Patients should be advised to discontinue tobacco use.

**Laboratory Tests**
Baseline laboratory data should be obtained prior to initiation of therapy. The hematologic status as indicated by hemoglobin, hematocrit, white blood count (WBC), differential, reticulocytes and platelets should be monitored closely - at least every 3 or 4 days.

Hepatic and renal evaluation are indicated prior to beginning therapy. Urinalysis, transaminase, alkaline phosphatase and blood urea nitrogen tests should be repeated at least weekly.

**Drug Interactions**
See WARNINGS section.

No cross-resistance with other chemotherapeutic agents, radiotherapy or steroids has been demonstrated.

**Carcinogenesis, Mutagenesis and Impairment of Fertility**
See WARNINGS section.

**Pregnancy**
See WARNINGS section.

**Nursing Mothers**
It is not known whether Matulane is excreted in human milk. Because of the potential for tumorigenicity shown for procarbazine hydrochloride in animal studies, mothers should not nurse while receiving this drug.

**Pediatric Use**
Undue toxicity, evidenced by tremors, coma and convulsions, has occurred in a few cases. Dosage, therefore, should be individualized (see DOSAGE AND ADMINISTRATION). Very close clinical monitoring is mandatory.

**ADVERSE REACTIONS**
Leukopenia, anemia and thrombocytopenia occur frequently. Nausea and vomiting are the most commonly reported side effects.

Other adverse reactions are:

**Hematologic**
Pancytopenia; eosinophilia; hemolytic anemia; bleeding tendencies such as petechiae, purpura, epistaxis and hemoptysis.

**Gastrointestinal**
Hepatic dysfunction, jaundice, stomatitis, hematremesis, melena, diarrhea, dysphagia, anorexia, abdominal pain, constipation, dry mouth.

**Neurologic**
Coma, convulsions, neuropathy, ataxia, paresthesia, nystagmus, diminished reflexes, falling, foot drop, headache, dizziness, unsteadiness.

**Cardiovascular**
Hypotension, tachycardia, syncope.

**Ophthalmic**
Retinal hemorrhage, papilledema, photophobia, diplopia, inability to focus.

**Respiratory**
Pneumonitis, pleural effusion, cough.

**Dermatologic**
Herpes, dermatitis, pruritus, alopecia, hyperpigmentation, rash, urticaria, flushing.

**Allergic**
Generalized allergic reactions.

**Genitourinary**
Hematuria, urinary frequency, nocturia.

**Musculoskeletal**
Pain, including myalgia and arthralgia; tremors.

**Psychiatric**
Hiccoughs, depression, apprehension, nervousness, confusion, nightmares.

**Endocrine**
Gynecomastia in prepubertal and early pubertal boys.

**Miscellaneous**
Intercurrent infections, hearing loss, pyrexia, diaphoresis, lethargy, weakness, fatigue, edema, chills, insomnia, slurred speech, hoarseness, drowsiness.

Second nonlymphoid malignancies (including lung cancer, acute myelogenous leukemia and malignant myelosclerosis) and azospermia have been reported in patients with Hodgkin’s disease treated with procarbazine in combination with other chemotherapy and/or radiation. The risks of secondary lung cancer from treatment appear to be multiplied by tobacco use.

**OVERDOSAGE**
The major manifestations of overdosage with Matulane would be anticipated to be nausea, vomiting, enteritis, diarrhea, hypotension, tremors, convulsions and coma.

Treatment should consist of either the administration of an emetic or gastric lavage. General supportive measures such as intravenous fluids are advised. Since the major toxicity of procarbazine hydrochloride is hematologic and hepatic, patients should have frequent complete blood counts and liver function tests throughout their period of recovery and for a minimum of two weeks thereafter. Should abnormalities appear in any of these determinations, appropriate measures for correction and stabilization should be immediately undertaken.

The estimated mean lethal dose of procarbazine hydrochloride in laboratory animals varied from approximately 150 mg/kg in rabbits to 1300 mg/kg in mice.

**DOSAGE AND ADMINISTRATION**
The following doses are for administration of the drug as a single agent. When used in combination with other anticancer drugs, the Matulane dose should be appropriately reduced, eg. in the MOPP regimen, the Matulane dose is 100 mg/m² daily for 14 days. All dosages are based on the patient's actual weight. However, the estimated lean body mass (dry weight) is used if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention.

**Adults**
To minimize the nausea and vomiting experienced by a high percentage of patients beginning Matulane therapy, single or divided doses of 2 to 4 mg/kg/day for the first week are recommended. Daily dosage should then be maintained at 4 to 6 mg/kg/day until maximum response is obtained or until the white blood count falls below 4000/mm³ or the platelets fall below 100,000/mm³. When maximum response is obtained, the dose may be maintained at 1 to 2 mg/kg/day. Upon evidence of hematologic or other toxicity (see PRECAUTIONS section), the drug should be discontinued until there has been satisfactory recovery. After toxic side effects have subsided, therapy may then be resumed at the discretion of the physician, based on clinical evaluation and appropriate laboratory studies, at a dosage of 1 to 2 mg/kg/day.

**Pediatric Patients**
Very close clinical monitoring is mandatory. Undue toxicity, evidenced by tremors, coma and convulsions, has occurred in a few cases. Dosage, therefore, should be individualized. The following dosage schedule is provided as a guideline only.

Fifty (50) mg per square meter of body surface per day is recommended for the first week. Dosage should then be maintained at 100 mg per square meter of body surface per day until maximum response is obtained or until leukopenia or thrombocytopenia occurs. When maximum response is attained, the dose may be maintained at 50 mg per square meter of body surface per day. Upon evidence of hematologic or other toxicity (see PRECAUTIONS section), the drug should be discontinued until there has been satisfactory recovery, based on clinical evaluation and appropriate laboratory tests. After toxic side effects have subsided, therapy may then be resumed.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 1-6 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**HOW SUPPLIED**
Capsules, ivory, containing the equivalent of 50 mg procarbazine as the hydrochloride; supplied in bottles of 100 (NDC 54482-053-01). Imprint on capsules: MATULANE ( ) sigma-tau.

**REFERENCES**
3. National Study Commission on Cytotoxic Exposure: Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, ScD, Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.

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