PRODUCT MONOGRAPH

[Pr]Matulane®

Procarbazine hydrochloride

50 mg Capsules

USP

Antineoplastic agent

Leadiant Biosciences, Inc.
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Scarborough, Ontario
M1H 2W4

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Control # 206969

® Registered Trade Mark

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[Pr]Matulane®

Procarbazine hydrochloride

PART I: HEALTH PROFESSIONAL INFORMATION

CAUTION

MATULANE (PROCARBAZINE HYDROCHLORIDE) IS A POTENT DRUG AND SHOULD ONLY BE USED BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE PERFORMED REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW OR ABNORMAL RENAL OR HEPATIC FUNCTION IS SEEN. CAPSULES SHOULD NOT BE OPENED.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	50 mg capsule	Not Applicable. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Matulane (procarbazine hydrochloride) is indicated for use in combination with other anticancer agents for the treatment of Stage III and IV Hodgkin's disease. Matulane is used as part of the MOPP (mechlorethamine, vincristine, procarbazine, prednizone) regimen.

Matulane has also been used successfully alone or in combination with other chemotherapeutic agents to produce regression in a variety of tumour types such as lymphomas and gliomas but data are not yet sufficient to justify specific recommendations.

CONTRAINDICATIONS

- hypersensitivity to procarbazine or any other component of the product.
- inadequate marrow reserve as demonstrated by bone marrow aspiration. Due consideration of this possible state should be given to each patient who has leukopenia, thrombocytopenia or anemia.

WARNINGS AND PRECAUTIONS

Matulane (procarbazine hydrochloride) should be prescribed by a qualified health care professional who is experienced with cancer chemotherapy drugs. Clinically significant treatment- related toxicities include:

- **Long-term risk of developing acute leukemia, myelodysplasia, second cancers**
- **Infertility**
- **Neuropathy**
- **MAO (monoamine oxidase) inhibition**

The MOPP regimen is not recommended in treating favourable prognosis CS I-II patients.

General

It is recommended that Matulane (procarbazine hydrochloride) be given only by or under the supervision of a physician experienced in the use of potent antineoplastic drugs. Adequate clinical and laboratory facilities should be available for a proper monitoring of a treatment.

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 a disulfiram-like reaction.

Because Matulane exhibits some monoamine oxidase inhibitory activity, sympathomimetic drugs, tricyclic antidepressant drugs (e.g. amitriptyline hydrochloride, imipramine hydrochloride), and other drugs, dietary supplements (e.g. ginseng) and foods known to react with momoamine oxidase inhibitors due to high tyramine content or other physiologic properties should be avoided. High tyramine content is most common in foods that are aged or fermented to increase flavor such as cheeses, yeast or meat extracts, fava or broad bean pods, smoked or pickled meat, poultry, or fish, fermented sausage (bologna, pepperoni, salami, and summer sausage) or other unfresh meat, or dried or overripe fruit.

A further phenomenon of toxicity common to many hydrazine derivatives is hemolysis and the appearance of Heinz-Ehrlich inclusion bodies in erythrocytes.

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, neuropathies or confusion.
- Leukopenia (white blood count under 4,000).
- Thrombocytopenia (platelets under 100,000).
- Hypersensitivity reaction.
- Stomatitis - The first small ulceration or persistent spot soreness around the oral cavity is a signal for cessation of therapy.
- Diarrhea - Frequent bowel movements or watery stools.
- Hemorrhage or bleeding tendencies.

Therapy may be resumed, at the discretion of the physician, after toxic side effects have cleared on clinical evaluation and appropriate laboratory studies.

Carcinogenesis and Mutagenesis

Instances of new 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.

The international population-based study Hodgkin Lymphoma patients has demonstrated statistically significant risk of acute myeloid leukemia following Hodgkin lymphoma treatments over a 30-year period [Schonfeld, 2006]. One-year Hodgkin lymphoma survivors (N = 35,511) were identified within 14 population-based cancer registries in Nordic countries and North America from January 1, 1970, through December 31, 2001. A total of 217 Hodgkin lymphoma survivors were diagnosed with AML. The excess absolute risk of AML declined statistically significantly after 1984 (7.0 to 4.2 and 16.4 to 9.9 in the < 35 and ≥ 35 age groups, respectively, which may be associated with modifications in chemotherapy. Analytical studies with detailed treatment data are required to correlate these decreases with changes in therapy and to better understand the long term risk of AML after Hodgkin’s Lymphoma.

The carcinogenicity of procarbazine hydrochloride in animals and mutagenicity in test systems has been reported in a number of studies (see TOXICOLOGY).

Hematologic

Leukopenia and thrombocytopenia have been reported in patients on Matulane therapy. Platelets and white blood cell counts should be performed prior to each subsequent cycle.

Hepatic/Renal

Undue 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.

The metabolism of procarbazine is dependent on hepatic transformation and renal elimination. Therefore, dosing modifications may be required in patients with compromised renal or hepatic function.

Sexual Function/Reproduction

Exposure to procarbazine has been reported to be an independent risk factor for acute ovarian failure and acute amenorrhea in females. Azoospermia which can be prolonged resulting in male infertility has been reported to be associated with procarbazine when used in combination with other chemotherapeutic agents.

The standard battery of fertility/reproduction studies in laboratory animals have not been carried out with procarbazine hydrochloride (see TOXICOLOGY).

Special Populations

Pregnancy: 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. Procarbazine is teratogenic, mutagenic, and carcinogenic. 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 was found to be teratogenic in animal studies (see TOXICOLOGY). Procarbazine hydrochloride has not been adequately studied in animals for its effects on peri- and postnatal development. However, neurogenic tumours were noted in the offspring in animal studies (See TOXICOLOGY).

***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: Appropriate prospective controlled studies in the pediatric population have not been performed. Undue toxicity, evidenced by tremors, coma and convulsions, has occurred in a few cases. Dosage, therefore, should be individualized. Very close monitoring is mandatory.

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

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

As part of routine monitoring clinical pulmonary exam, including auscultation, pulmonary toxicity ratings (Cough, SOB) should be performed periodically.

***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 and tricyclic antidepressants (e.g. amitriptyline HCl, imipramine HCl) should not be used. 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.

ADVERSE REACTIONS

In dealing with cancer chemotherapeutic agents, adverse effects are not only common but are to be expected, and actually serve as a guideline to dosage and duration of administration; Matulane (procarbazine hydrochloride) is no exception as to toxicity.

The following adverse reactions include both adverse experiences from clinical trials as well as post-marketing surveillance.

The most serious adverse effects are associated with leukopenia, thrombopenia and a variety of neurological effects (MAO inhibition).

The most commonly reported adverse effects are nausea and vomiting. Leukopenia, anemia and thrombopenia occur frequently.

Other adverse reactions grouped by Body System:

Hematologic: Immunosuppression, pancytopenia, eosinophilia, hemolytic anemia, bleeding tendencies such as petechiae, purpura, epistaxis and hemoptysis; thrombosis including pulmonary, deep vein, and mesenteric.

Gastrointestinal: Hepatic dysfunction, jaundice, stomatitis, ascites, hematemesis, melena, diarrhea, dysphagia, anorexia, abdominal pain, constipation, dry mouth, pancreatitis.

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

Cardiovascular: Hypotension, tachycardia, syncope, hypertension, angina, pericarditis, cardiotoxicity, Raynaud-like syndrome.

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

Respiratory: Pneumonitis, pleural effusion, cough, pneumonia, pulmonary toxicity.

Dermatologic: Herpes, dermatitis, pruritus, alopecia, hyperpigmentation, rash, urticaria, flushing, photosensitivity, Lyell syndrome, toxic epidermal necrolysis.

Allergic: Generalized allergic reactions.

Genitourinary: Hematuria, urinary frequency, nocturia, nephritis.

Musculoskeletal: Pain, including myalgia and arthralgia; tremors, osteonecrosis.

Psychiatric: Hallucinations, depression, apprehension, nervousness, confusion, nightmares, insomnia.

Endocrine: Acute ovarian failure, acute amenhorrhea, gynecomastia in prepubertal and early pubertal boys.

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

Second malignancies (including lung cancer, acute myelocytic leukemia and malignant myelosclerosis) and azoospermia 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.

DRUG INTERACTIONS

Matulane (procarbazine hydrochloride) is used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastrointestinal effects (see WARNINGS AND PRECAUTIONS).

Drug-Drug Interactions

CNS depression and possible potentiation may occur with barbiturates, antihistamines, narcotics, hypotensive agents, phenothiazines, momoamine oxidase (MAO) inhibitors, or catechol-O-mthyltransferase (COMT) inhibitors. Matulane can interfere with the absorption of digoxin. The effects of antidiabetics and levodopa may be enhanced by Matulane use. Sensitivity to Matulane can be increased when used with carbamazepine. Concomitant use of these drugs with Matulane should be avoided. Matulane also exhibits monoamine oxidase inhibitory activity. Sympathomimetic drugs and tricyclic antidepressant drugs may interact with Matulane to cause hypertensive reactions (see WARNINGS AND PRECAUTIONS).

Drug-Food Interactions

Dietary supplements or foods known to react with monoamine oxidase inhibitors due to high tyramine content or other physiologic properties should be avoided (see WARNINGS AND PRECATIONS). Typical reactions include headache, flushed face, palpitations, nausea and vomiting or hypertension.

DOSAGE AND ADMINISTRATION

Matulane (procarbazine hydrochloride) should only be used by physicians experienced with cancer chemotherapeutic drugs.

As part of the MOPP (mechlorethamine, vincristine, and prednisone) and c-MOPP (cyclophosphamide, mechlorethamine, vincristine, and prednisone) regimens Matulane is given orally in a dose of 100mg/m^2/day for 14 days and repeated every 4 weeks.

Upon evidence of hematologic or other toxicity (see WARNINGS 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.

OVERDOSAGE

The major manifestations of overdosage with Matulane (procarbazine hydrochloride) 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.

ACTION AND CLINICAL PHARMACOLOGY

Matulane (procarbazine hydrochloride) is one of the methylhydrazine derivatives that has demonstrated an antineoplastic effect against Hodgkin's Disease. The mode of cytotoxic action of Matulane has not yet been clearly defined; however, there is evidence that the drug may act by inhibition of protein, RNA and DNA synthesis. No cross resistance with other chemotherapeutic agents, radiotherapy or steroids has been demonstrated.

Pharmacokinetics:

Procarbazine hydrochloride is metabolized primarily in the liver and kidneys. The drug appears to be auto-oxidized to the azo derivative with the release of hydrogen peroxide. The azo derivative isomerizes to the hydrazone, and following hydrolysis splits into a benzylaldehyde derivative and methylhydrazine. The methylhydrazine is further degraded to CO_2 and CH_4 and possibly hydrazine, whereas the aldehyde is oxidized to *N*-isopropylterephthalamic acid, which is excreted in the urine. Procarbazine hydrochloride is rapidly and completely absorbed. Following oral administration of 30 mg of ^{14}C-labeled procarbazine hydrochloride, maximum peak plasma radioactive concentrations were reached within 60 minutes.

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

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

STORAGE AND STABILITY

Matulane (procarbazine hydrochloride) should be stored at 15 - 30°C in a tightly closed, light resistant container.

SPECIAL HANDLING INSTRUCTIONS

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. Patients and patient caregivers should not open or crush capsules. Do not take Matulane if the capsule is broken. Keep out of reach of children.

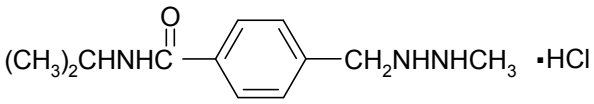
DOSAGE FORM, COMPOSITION AND PACKAGING

Matulane (procarbazine hydrochloride) Capsules: 100 size No. 2 ivory gelatin capsules containing 50 mg procarbazine incorporated as procarbazine hydrochloride in a plastic bottle. Inactive ingredients (alphabetical order): cornstarch, gelatin, mannitol, methylparaben, potassium sorbate, propylparaben, quinoline yellow WS, sunset yellow FCF, talc, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Structural Formula:



Molecular Formula: $C_{12}H_{19}N_3O$•HCl

Molecular Weight: 257.76

Chemical Name: *N*-isopropyl-alpha-(2-methylhydrazino)-*p*-toluamide monohydrochloride.

Appearance: It is a white to pale yellow crystalline substance.

Solubility: Soluble but unstable in water or aqueous solutions.

CLINICAL TRIALS

Original sponsor generated clinical trial data are not available; however, for information regarding efficacy in Hodgkin's disease refer to the published literature, for example:

Bonadonna G, Viviani S, Bonfante V, Gianni AM, Valagussa Survival in Hodgkin's disease patients--report of 25 years of experience at the Milan Cancer Institute. Eur J Cancer. 2005 May;41(7):998-1006. Epub 2005 Feb 24.

Longo DL, Young RC, Wesley M, Hubbard SM, Duffey PL, Jaffe ES, DeVita VT Jr. Twenty years of MOPP therapy for Hodgkin's disease. J Clin Oncol. 1986 Sep; 4(9):1295-306.

DETAILED PHARMACOLOGY

Procarbazine is a unique antineoplastic agent with multiple sites of action. It belongs to N-methyl anti-tumor agents which are inactive prodrugs, require conversion to tumorstatic active metabolites. Oral absorption of procarbazine is rapid and complete. Mean maximum plasma concentration in humans is 12.5 min.

The elimination rate of procarbazine from plasma is high. The mean apparent oral systemic clearance and the plasma elimination half-life are 38.8 L/min and 9.2 min, respectively. Considerable amounts of azo-procarbazine are found in human plasma. The mean Cmax and AUC ratios of azo-procarbazine /procarbazine are 5.5 and 45.2. Procarbazine is oxidized by both mitochondrial monoamine oxidase and hepatic microsomal cytochrome P450 iso-enzymes. Azo-procarbazine is formed very rapidly from procarbazine, but eliminated much more slowly from plasma than procarbazine. Considerable interindividual differences in the conversion rate of azo-procarbazine should have consequences for the individual tumor therapeutic efficiency of procarbazine.

Distribution of the drug in body fluids, studies in dog and man, showed rapid equilibration between plasma and cerebrospinal fluid after oral administration. Pharmacological studies indicated excellent gastrointestinal absorption. The major portion of the drug was excreted in the urine as N-isopropyl-terephthalamic acid with approximately 25 to 42 percent appearing during the first 24 hours after administration.

In laboratory studies, procarbazine hydrochloride produced a variety of biologic effects. Among these have been immuno-suppression, teratogenesis, carcinogenesis, cytotoxicity with mitotic suppression and chromatin derangement and an antineoplastic effect against a spectrum of transplanted tumours in mice and rats.

The major drug toxicities in acute and chronic animal studies were hematologic with granulocyte depression, thrombocyte depression, anemia and hemolysis.

Reticuloendiothelial system lymphocytic depletion, marrow cell depression, testicular atrophy and mucous membrane ulceration were further evidence of in vivo cytotoxicity.

TOXICOLOGY

The oral LD_{50} of procarbazine hydrochloride in rabbits and mice was determined to be 150 to 1300 mg/kg respectively. The carcinogenicity of procarbazine hydrochloride in mice, rats and monkeys has been reported in a considerable number of studies. Mammary adenocarcinomas in rats have been observed subsequent to procarbazine hydrochloride administration in high doses. Carcinogenicity studies performed with procarbazine hydrochloride in the 1960's revealed that multiple pulmonary tumors and leukemia were induced in mice by single and repeated intraperitoneal or oral administration. Instances of new 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. Recent clinical findings suggest that the risks of secondary lung cancer from treatment appears to be multiplied by tobacco use.

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

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. Procarbazine hydrochloride has not been adequately studied in animals for its effects on peri- and postnatal development. However, neurogenic tumours were noted in the offspring of rats given intravenous injections of 125 mg/kg of procarbazine hydrochloride on day 22 of gestation.

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.

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PART III: CONSUMER INFORMATION

PrMatulane®
procarbazine hydrochloride capsules

This leaflet is part III of a three-part "Product Monograph" published when Matulane was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Matulane. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Matulane is used to treat Stage III and IV Hodgkin's disease in combination with certain cancer drugs. Matulane is used as part of the MOPP regimen (nitrogen mustard, vincristine, procarbazine, prednisone).

What it does:
Matulane is thought to work by killing rapidly dividing cells, such as cancer cells.

When it should not be used:
- allergic to procarbazine hydrochloride or any of the other ingredients in Matulane**.**
- have low blood cell counts (bone marrow depression).

What the medicinal ingredient is:
Procarbazine hydrochloride.

What the nonmedicinal ingredients are:
Cornstarch, gelatin, mannitol, methylparaben, potassium sorbate, propylparaben, quinoline yellow WS, sunset yellow FCF, talc, and titanium dioxide.

What dosage it comes in:
Matulane is available in capsules. Each capsule contains 50 mg of procarbazine as procarbazine hydrochloride.

WARNINGS AND PRECAUTIONS

Matulane should be prescribed and managed by a doctor experienced in the use of anti-cancer drugs.
Serious side effects with the use of Matulane include:
- long-term risk of acute leukemia (blood cancer), myelodysplasia (a decrease of the production of blood cell), and developing another type of cancer
- infertility
- neuropathy (nerve damage)
- Monoamine oxidase (MAO) inhibition

The MOPP regimen is not recommended to treat early stages of Hodgkin's disease.

Before you use Matulane talk to your doctor if any of the following applies to you:

- if you have or have experienced a sensitivity or allergic reaction to Matulane or any component of the product.
- if you have low blood cell counts due to bone marrow problems.
- if you have kidney or liver disease.
- if you are pregnant or planning to be pregnant, and if you are breastfeeding.

Matulane may cause sterility in men and menopause in women.

Matulane may damage sperm and may harm your baby if used during pregnancy. Effective birth control methods must be used while taking Matulane.

Do not smoke, as Matulane may increase the risk of developing lung cancer in patients who smoke.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about other medications or dietary supplements that you are taking as your dose may need to be changed. Check with your doctor or pharmacist before you start taking any new drugs or dietary supplements. Matulane in combination with barbiturates, antihistamines, narcotics, hypotensive agents or phenothiazines may cause CNS depression (slowing of normal brain function) and increase the effect of these medications. Matulane can interfere with the absorption of digoxin. The effects of antidiabetics and levodopa may be enhanced by Matulane use. Sensitivity to Matulane can be increased when used with carbamazepine. Matulane also exhibits monoamine oxidase inhibitory activity. Dietary supplements (e.g. ginseng) and foods known to react with momoamine oxidase inhibitors should be avoided. Sympathomimetic drugs (such as cold remedies) and tricyclic antidepressant drugs may interact with Matulane to cause a rise in blood pressure.

Alcohol may interact with Matulane, causing flushing, headache or sweating. Do not drink alcohol, alcohol-free or reduced-alcohol beer or wine while being treated with Matulane.

Avoid certain foods which have a substance called tyramine as it may interact with Matulane. Typical reactions include headache, flushed face, palpitations, nausea and vomiting or a rise in blood pressure. Do not eat foods that have a high tyramine content (most common in foods that are aged or fermented to increase their flavor), such as cheeses, yeast or meat extracts, fava or broad bean pods, smoked or pickled meat, poultry, or fish, fermented sausage (bologna, pepperoni, salami, and summer sausage) or other unfresh meat, or any dried or overripe fruit. Do not eat or drink large amounts of caffeine-containing food or beverages, such as chocolate, coffee, tea, or cola.

Talk to your doctor about tyramine containing foods for a complete list.

PROPER USE OF THIS MEDICATION

Your doctor will determine the length of your treatment based on your treatment goals, the medicines you receive, and how your body responds to those medicines.

Matulane is usually given in cycles that include rest periods between treatments. The rest periods give your body a chance to build healthy cells and regain your strength before the next treatment.

It is important to take Matulane exactly as directed by your doctor. Make sure you understand the directions.

Do not open or crush capsules. Do not take Matulane if the capsule is broken.

Overdose:

Do not take more than the prescribed dose (see Missed Dose below). Symptoms of overdose may occur as nausea, vomiting, diarrhea, low blood pressure, tremors, convulsions, and coma. Contact your Poison Control Center for information and management information.

Missed Dose:

If you miss a dose of Matulane, take it as soon as you can if it is within 12 hours of the missed dose. If it is over 12 hours since your missed dose, skip the missed dose and go back to your usual dosing times. Call your doctor to ask about making up the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In dealing with cancer drugs, adverse effects are not only common but are to be expected and actually serve as a guideline to dosage and duration of administration.

The most serious adverse effects are associated with changes in blood cell counts and a variety of neurological effects such as headache, flushing of the face, palpitations, and rise in blood pressure.

The most common reported adverse effects are nausea and vomiting. Changes in blood cell counts occur frequently.

The following side effects have also been reported: infection or reduced ability to fight infection, excessive bleeding, blood clots, liver function changes, coma, convulsions (seizures), headache, nerve or reflex problems, low or high blood pressure, chest pain, heart damage, vision changes, cough, lung infection and lung damage, skin reactions (sometimes serious), allergic reactions, urinary disturbances, pain, weakness, depression, nervousness, nightmares, fever, sweating, chills, and hallucinations.

Check with your doctor immediately if any of these side effects occur:

- Central nervous system signs or symptoms such as tingling, numbness or confusion
- Reduced white blood cell count
- Reduced platelet count
- Allergic reactions
- The first small ulceration or persistent spot soreness around the mouth
- Diarrhea- frequent bowel movements or watery stools
- Excessive or abnormal bleeding

Second cancers and male and female reproductive effects have been reported in patients with Hodgkin's disease treated with Matulane in combination with other cancer drugs and/or radiation.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Common	Reduced white blood cell count		√
	Infection or reduced ability to fight infection		√
	Reduced platelet count		√
	Excessive or abnormal bleeding		√

Uncommon	Central nervous system signs or symptoms such as tingling, numbness or confusion		√
	Allergic reactions		√
	The first small ulceration or persistent spot soreness around the mouth		√
	Diarrhea- frequent bowel movements or watery stools		√
	Blood clots		√
	Liver function changes		√
	Coma		√
	Convulsions (seizures)		√
	Low or high blood pressure		√
	Chest pain (possible heart damage)		√
	Vision changes		√
	Lung infection (possible lung damage)		√
	Skin reactions		√
	Urinary disturbances		√
	Hallucinations		√

This is not a complete list of side effects. For any unexpected effects while taking Matulane, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach of children. Store away from heat and direct light. Store at 15° - 30°C. Protect from light. Do not store in the bathroom, near the kitchen sink, or in other damp places.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effects, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Leadiant Biosciences, Inc. at: 1-800-447-0169.

This leaflet was prepared by Leadiant Biosciences, Inc.

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