

PRESCRIBING INFORMATION

AMSA PD*

Amsacrine Injection

**75 mg/1.5 ml Ampoule
(50 mg/ml)**

ANTINEOPLASTIC AGENT



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CONTROL NUMBER: 100449

PRESCRIBING INFORMATION**AMSA PD****AMSACRINE INJECTION****75 mg Ampoule**

CAUTION: AMSA PD IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). FACILITIES SHOULD BE AVAILABLE FOR THE MANAGEMENT OF BONE MARROW SUPPRESSION. PERIODIC MONITORING OF BONE MARROW AND PERIPHERAL BLOOD SHOULD BE DONE. IN ADDITION LIVER AND RENAL FUNCTION MUST BE EVALUATED, PRIOR AND DURING AMSA PD THERAPY.

PHARMACOLOGICAL CLASSIFICATION

Antineoplastic Agent

ACTION AND CLINICAL PHARMACOLOGY

AMSA PD is a potent cytotoxic agent. In in vitro studies, the LD₅₀ against cultured L1210 cells is 0.04 µg/ml and 0.2 µg/ml against cultured Novikoff cells at six hours. Higher concentrations or longer exposure produce cell destruction. A three-hour exposure of Novikoff cells to 2 µg of AMSA PD indicated 62% inhibition of DNA synthesis (incorporation of radioactive thymidine) while RNA synthesis was not affected (incorporation of radioactive uridine). Essentially the same results were obtained in vivo when L1210-inoculated mice were treated with a dose of 0.1 mg/mouse. AMSA PD binds to DNA both through intercalation and external binding and has base specificity for A-T pairs.

Cycling cells are two to four times more sensitive to AMSA PD than are resting cells. Cycling cells initially in S and G2 phases were grossly delayed in their capacity for normal progression, leading to a transitory (approximately eight hours) accumulation of cells in S phase, followed at later times by arrest in G2 phase. A limited degree of mitotic nondisjunction and a high degree of polyploidization was seen. Examination of chromosome damage indicated incomplete condensation and chromosome stickiness, which are characteristics of DNA intercalators.

AMSA PD is active against a wide spectrum of murine tumors. These include the ascitic form of L1210 and P388 leukemias, Lewis lung carcinoma, spontaneous C₃H mammary adenocarcinoma, mammary tumor in CD8F mice, and the commonly resistant B16 melanoma. No antitumor activity was detected in intracerebrally inoculated L1210 leukemia, which suggests that AMSA PD penetration across the blood-brain barrier in mice did not achieve significant levels.

The effect of AMSA PD on the immune system was also investigated. The production of hemolytic plaque-forming cells (PFC) in mice in response to immunization with sheep red blood cells (SRBC) was used as the indicator of activity. In contrast to the 95% inhibition of PFC formation caused by Actinomycin D, cyclophosphamide, cytosine arabinoside, thioguanine and vinblastine, AMSA PD produced no such inhibition when administered at the same time as SRBC. However, when given 28 hours following SRBC immunization, AMSA PD caused a 99% suppression of immune activity. After six days, the inhibition was still strongly evident.

Following a 90 mg/m² infusion of AMSA PD over 60 minutes, the plasma concentration showed a biphasic decrease with an alpha phase half-life of 10 to 15 minutes and a beta phase half-life of 8 to 9 hours. Peak plasma levels were dose dependent, increasing from 0.47 to 12.3 μM as the patient's dose was escalated from 10 to 90 mg/m².

In two studies, 15 of 54 (27.8%) evaluable patients achieved remission (7 were complete remissions and 8 were partial remissions). Duration of AMSA PD remissions is brief and variable if not followed by consolidation or maintenance regimens.

INDICATIONS

AMSA PD is indicated for induction of remission in acute adult leukemia refractory to conventional therapy.

CONTRAINDICATIONS

AMSA PD is contraindicated in patients who are hypersensitive to amsacrine, acridine derivatives (e.g., acriflavine), or to any component of this medication.

AMSA PD therapy is contraindicated in patients who have pre-existing drug-induced or radiotherapy-induced bone marrow suppression.

AMSA PD treatment is not contraindicated in patients who have received previous treatment with doxorubicin or daunorubicin.

WARNINGS

1. AMSA PD is a potent bone marrow suppressant. In some patients prolonged bone marrow aplasia may occur, necessitating intensive supportive therapy. Patients receiving AMSA PD must be under close medical supervision by physicians skilled in cancer chemotherapy. During induction therapy, leukocyte and platelet count determinations are mandatory and should be performed frequently especially during the two to three week period following administration of the drug. With recommended dose schedules, Leukopenia is usually transient, reaching its nadir at 11 to 13 days after treatment, with recovery usually occurring by the 17th to 25th day (see Dosage and Administration section). Leukocyte counts as low as $1000/\text{mm}^3$ can be expected during AMSA PD therapy. Red cell and platelet concentrations should be monitored because they also may be depressed. Doses higher than those recommended may produce more severe or more prolonged marrow suppression.

2. Facilities should be available for management of complications of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia). Periodic monitoring of bone marrow should be performed. Hematologic toxicity may require dose reduction, suspension, or delay of AMSA PD therapy.
3. Toxicity at recommended doses of AMSA PD is enhanced by hepatic or renal impairment. Laboratory evaluation of hepatic and renal function is necessary prior to and during administration. Liver metabolism and biliary excretion appear to be the major routes of AMSA PD elimination in man. Therefore, dose reduction is recommended in patients with significant hepatic dysfunction (bilirubin >2 mg/dl). The same recommendation applies in cases of significant renal impairment (BUN > 20 mg/dl), (creatinine >1.2 mg/dl), since 35% of the total dose is excreted by the kidney within 72 hours after administration (20% as intact drug).
4. There is no clear evidence from animal studies and clinical trials that AMSA PD is cardiotoxic. There have been eight documented cases in which an acute arrhythmia developed during or immediately after AMSA PD infusion. Several of these patients had received prior anthracycline treatment or were hypokalemic. An additional seven cases have been reported but no documentation is available. Therefore, careful monitoring of cardiac rhythm, during and after drug administration, is strongly recommended.
5. Patients with hypokalemia are at increased risk of ventricular fibrillation. The risk of developing arrhythmias can be minimized by ensuring a normal serum potassium level immediately prior to and during AMSA PD administration. Careful monitoring of cardiac rhythm is recommended for detection of cardioactivity. Fluid or electrolyte imbalance should be corrected prior to AMSA PD administration.
6. Use caution in handling and preparing the AMSA PD solution. The use of gloves, gown and eye protection are recommended. (See **DOSAGE AND ADMINISTRATION: General Information for the Safe Handling of Cytotoxic Agents**).

7. Pregnancy and Lactation: Safe use of AMSA PD in pregnancy has not been established. Reproduction studies have not been performed in animals. Thus, there is no evidence as to whether this drug may adversely affect fertility in either men or women or have teratogenic or other adverse effects on the fetus and embryo. Therefore, benefit/risk considerations should be carefully weighed in using AMSA PD in pregnant women or in patients of either sex in the reproductive age group. Women of childbearing potential should be advised to avoid becoming pregnant while receiving AMSA PD.

It is not known if AMSA PD is excreted in breast milk. Therefore, breast-feeding should be discontinued before receiving AMSA PD.

8. Use in the Elderly: Safety and effectiveness in the elderly have not been established.

PRECAUTIONS

1. Like other cytotoxic drugs, AMSA PD may induce hyperuricemia secondary to rapid lysis of neoplastic cells. Careful monitoring of the patient's blood uric acid level should be performed. Consideration may be given to reducing uric acid levels prophylactically, prior to or concurrent with AMSA PD treatment.
2. Pregnancy. See Warnings - Section regarding usage in Pregnancy.

Drug Interaction

1. Data available suggest that AMSA PD does not potentiate the increased risk of doxorubicin-induced cardiac toxicity.
2. Although animal studies suggested cross resistance between the anthracyclines and AMSA PD, clinical studies indicate that this is not true.
3. Sufficient data are not available to prove or disprove AMSA PD potentiation of the toxicities of other anticancer drugs.
4. Concomitant influenza or pneumococcal vaccination and immunosuppressive therapy have been associated with impaired immune response to the vaccine. Antineoplastic agents may increase the likelihood of infections following live virus vaccines. Therefore, live virus vaccines should thus be avoided.
5. AMSA PD may be displaced from serum albumin, with consequential increase in free drug and toxicity if used with other protein bound drugs.
6. Adverse effects may be potentiated by use with other cytotoxic agents.

Laboratory Tests: Complete blood counts, liver and renal function tests, and electrolytes should be performed regularly. Electrolytes should be re-evaluated before each day's treatment.

ADVERSE REACTIONS

The major toxicities associated with AMSA PD have been myelosuppression and mucositis. AMSA PD is a potent myelosuppressive drug and pancytopenia usually persists for about three weeks after administration. Hemorrhage may occur during this period and severe or life-threatening infections may be experienced. Pyrexia, apparently unrelated to sepsis, has been reported. Other target organ systems of toxicity are the gastrointestinal tract and central nervous system. Evidence of cumulative toxicity has not been observed.

Blood and Lymphatic System Disorders: myelosuppression is rapid in onset, and is consistent with the requirement to produce significant bone marrow hypoplasia to achieve a response. Using recommended doses and schedules, leukopenia occurs in most patients. Mild to severe anemia and mild to moderate thrombocytopenia also develop in the majority of patients. Patients with leukemia have pancytopenia due to the disease state as well as to prior therapy. While the goal of AMSA PD therapy is myelosuppression, this can become an untoward effect if therapy is prolonged. Also granulocytopenia.

Cardiac Disorders: congestive heart failure, bradycardia, tachycardia, and ventricular arrhythmias. Cardiac arrhythmias, such as sinus tachycardia or atrial fibrillation, may occur. Fatal or life threatening ventricular fibrillation, usually in patients with hypokalemia, has been reported. Cardiomyopathy has been reported in patients who had generally been pre-treated with anthracycline antibiotics. (See **WARNINGS** Section)

Gastrointestinal Disorders: gastrointestinal effects reported in over 10% of patients in decreasing order of frequency are: nausea, vomiting, stomatitis, diarrhea, perirectal abscess, and abdominal pain. Stomatitis (mucositis) has been reported as a serious side effect at higher dose levels. Other effects include dysphagia, hematemesis, gum hemorrhage, and gingivitis.

General Disorders and Administration Site Conditions: fever, asthenia, lethargy, cutaneous inflammatory reaction and inflammation at the injection site and death have occurred.

Hepatobiliary Disorders: hepatotoxicity, jaundice, hepatitis, hepatic insufficiency, and increased bilirubin. Jaundice and increased bilirubin effects are usually transient and return to normal after cessation of drug therapy. One death has been attributed to progressive liver failure.

Infections and Infestations: infection.

Investigations: elevated bilirubin elevated BUN, elevated alkaline phosphatase, elevated creatinine, elevated SGOT, ejection fraction decrease and ECG changes.

Metabolism and Nutrition Disorders: weight decrease, weight increase, anorexia

Musculoskeletal and Connective Tissue Disorders: musculoskeletal pain.

Nervous System Disorders: headache, paresthesias, hypoesthesia and dizziness. Seizures occurred in several patients, all of whom had metabolic conditions that may have caused the seizures or made these patients more susceptible to them.

Psychiatric Disorders: Emotional liability, confusion.

Renal and Urinary Disorders: hematuria, proteinuria. Renal failure has occasionally been reported.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea.

Skin and Subcutaneous Tissue Disorders: alopecia, urticaria, rashes (purpuric or maculopapular), purpura and dermatologic/allergic reaction.

Vascular Disorders: phlebitis, hemorrhage, hypotension. Phlebitis, related to the concentration of AMSA PD administered, is reduced by infusing the diluted drug over a period of 60 to 120 minutes (see Dosage and Administration Section).

Symptoms and Treatment of Overdosage

Hemorrhage and infection, resulting from bone marrow hypoplasia or aplasia, may require intensive supportive treatment with red cell, granulocyte, or platelet transfusions and appropriate antibiotics. Vigorous symptomatic treatment may be necessary for severe mucositis, vomiting, or diarrhea.

DOSAGE AND ADMINISTRATION

CAUTION: - AMSA PD MUST BE MIXED WITH THE L-LACTIC ACID DILUENT PROVIDED. THE RESULTANT SOLUTION MUST BE FURTHER DILUTED IN 500 ML DEXTROSE INJECTION, USP. DO NOT USE SALINE SOLUTIONS. AMSA PD IS INCOMPATIBLE WITH SOLUTIONS CONTAINING CHLORIDE IONS.

DOSAGE: FOR INTRAVENOUS INFUSION ONLY.

The following schedules are recommended for acute adult leukemia:

1. **Induction:** The total recommended dose for each five-day course of therapy is 375 to 625 mg/m². Each course is repeated at three-to-four-week intervals. Two courses may be necessary to achieve induction. This may be given according to the following schedules:

75 mg/m²/d x 5d; 100 mg/m²/d x 5d; and 125 mg/m²/d x 5d (the preferred regimen).

The dose of AMSA PD should be increased by 20% in the second and each subsequent course if the patient has had no significant toxicity in the preceding course, and if marrow hypoplasia has not been achieved. If patients have had life-threatening infection or hemorrhage during the preceding course, consideration should be given to decreasing the dose by 20%. Second and subsequent courses should not be initiated until recovery from drug-induced myelosuppression or evidence of residual leukemic infiltrate is evident.

2. **Maintenance:** Once remission has been achieved the maintenance dose should be about one half that described above, repeated every 4 to 8 weeks depending upon the peripheral blood counts and bone marrow recovery from myelosuppression.

ADMINISTRATION

Because of phlebitis that may occur at doses greater than 70 mg/m², AMSA PD must be diluted in 500 ml 5% Dextrose Injection USP and infused over a period of 60 to 90 minutes. Care must be taken that no extravasation occurs which could produce severe irritation or necrosis.

METHOD OF PREPARATION

Step One:

Each ampoule contains 75 mg (1.5 ml) of AMSA PD for infusion. Aseptically transfer 1.5 ml from the ampoule to the vial which contains 13.5 ml of L-lactic acid diluent (use only the diluent provided). The resulting orange-red solution is the STOCK SOLUTION which contains 5 mg AMSA PD per ml. It is preferable to use glass syringes for step one, however, plastic syringes can be used, providing that AMSA PD remains in the syringes for no longer than 15 minutes. The stock solution is chemically stable for 24 hours at room temperature when protected from exposure to direct sunlight. Since this solution does not contain a preservative, any unused portion should be discarded.

Step Two:

Prepare the intravenous infusion solution by aseptically transferring the total daily dose of STOCK SOLUTION to 500 ml Dextrose Injection USP. DO NOT USE SALINE SOLUTION. The freshly prepared intravenous infusion is chemically stable for up to 7 days when using an Abbott plastic container or glass bottle.

As with all intravenous admixtures containing no preservatives (microbiological) the solution should be used within 24 hours when stored at room temperature or 72 hours, when refrigerated.

Caution in the handling and preparation of the solution should be exercised, and the use of gloves is recommended. If AMSA PD solution contacts the skin or mucosa, immediately wash thoroughly with soap and water.

GENERAL INFORMATION FOR THE SAFE HANDLING OF CYTOTOXIC AGENTS

1. Preparation of all anti-neoplastic agents should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).
2. Personnel preparing parenteral anti-neoplastic agents should wear PVC gloves, safety glasses, disposable gowns and masks.
3. All needles, syringes, vials, ampoules, and other materials which have come in contact with cytotoxic drugs should be segregated and incinerate at 1000°C or more. Sealed containers may explode sealed. Intact vials or ampoules, unopened bottles, or oral medication should be returned to the Manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport. If incineration is not available, neutralization should be done (the Manufacturer can supply this information), usually with the use of 5% sodium hypochlorite and/or 5% sodium thiosulfate.
4. Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.

AVAILABILITY

AMSA PD for infusion is supplied in trays of five individual packages.

Each package contains one 75 mg ampoule of AMSA PD (50 mg/ml) in 1.5 ml of n, n-dimethyl acetamide, and one 13.5 ml vial of L-lactic acid diluent (0.0353M). Preservative free.

Store at controlled room temperature (15° – 25°C).

Information for the Patient

The patient should be instructed to report any signs of side effects. In addition, the patient should be instructed not to receive any vaccine, while receiving AMSA PD Therapy.

PHARMACEUTICAL INFORMATION**Drug Substance**

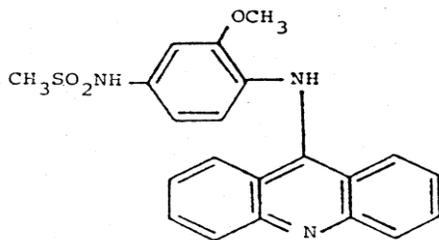
Common Name: Amsacrine

Chemical Name: N-[4-(acridin-9-ylamino)-3-methoxyphenyl 1]-methane sulfonamide. This compound is frequently referred to as m-AMSA,

Empirical Formula: C₂₁H₁₉N₃O₃S

Molecular Weight: 393.46

Structural Formula:



PHARMACOLOGY

Amsacrine is a yellow crystalline powder with a melting point range between 230° - 240°C.

In experimental animals, AMSA PD shows excellent antitumor activity, concentrates in the liver, and binds to melanin granules.

The cell inhibition studies with L1210 mouse leukemia showed about 60% inhibition of growth when 0.2 FM of AMSA PD HCl was present in the culture. Similar inhibition by proflavine and 9-Aminoacridine required 2 FM and 4 FM, respectively.

Based on cell kinetic data and chromosome damage studies, the cells initially in G₁ (postmitotic phase) or G₁ arrest during the period of exposure to AMSA PD HCl are most refractory to the cytotoxic effects of AMSA PD HCl and pose the greatest threat of being able to survive (after the initial drug treatment) and re-establish the tumor during the post-treatment period.

AMSA PD (methane sulfonate salt and free base) was also evaluated against the B16 malignant melanoma in mice. AMSA PD was active over a range of doses when administered IP daily for 9 days to mice previously implanted IP with tumor brei of B16. Doses as low as 0.80 mg/kg/injection were markedly effective in increasing life spans of drug-treated mice to 77% over the infected control mice dying from melanoma.

AMSA PD HCl (salt and base) was also evaluated against P388 lymphocytic leukemia in BDF₁ mice. Both forms of AMSA PD were highly active over a wide range of doses against P388 and moderate to good cures were obtained when higher doses of each forms of the drug were given every four days.

Combination chemotherapy studies against L1210 and P388 leukemia in mice with AMSA PD and cis-platinum or AMSA PD and piperazinedione showed improved therapeutic responses over that observed for each drug administered alone.

AMSA PD also has antiviral properties. At doses which were not cytotoxic for HeLa cells, AMSA PD protected against vaccinia virus cytotoxicity.

TOXICOLOGY**Intravenous toxicity**

Toxicity studies with AMSA PD (base) were conducted in mice, dogs, and monkeys. In mice, the range from LD₁₀ (91.2 mg/m²) to LD₉₀ (111.9 mg/m²). The monkey was more resistant to the toxic effects of AMSA PD. Drug toxicity was reduced when a given total dose was administered in smaller daily doses. With intravenous administration, AMSA PD (base) had toxic effects on the liver, kidney, lymphoid tissue, bone marrow, gastrointestinal tract, and central nervous system. Toxicity was most marked in the liver in all the experimental species.

Oral Toxicity

The oral toxicity of AMSA PD (base) was investigated in mice. The results are shown in the following table:

<u>Oral Toxicity of AMSA PD base mg/m²</u>			
MICE	LD ₁₀	LD ₅₀	LD ₉₀
Male	441	810	1488.6
Female	474	729	1117.0

AMSA PD was administered via gelatin to dogs in single and multiple treatment regimes. Dogs were given AMSA PD on a single-treatment schedule, at dosage of 62.5 mg/m² to 1000 mg/m². On a daily schedule for 5 days, AMSA PD was given at doses of 31.25 mg/m² to 500 mg/m². On the single dose schedule, one of two dogs died at 1000 mg/m²; on the multiple dose schedule, two of two dogs died at 500 mg/m². Dogs given the lethal dose (both schedules) had predominant lesions of the intestinal mucosa, bone marrow, hematopoietic tissue, and lymphoid organs. Below the lethal dose in the single treatment study, no lesions were seen.

Local Irritation

Local tissue reaction studies in guinea pigs and rabbits given 0.5 ml of AMSA PD subcutaneously or intramuscularly suggested that the acidity of the drug solution was responsible for most of the local tissue irritation. Topical application of AMSA PD to rabbits showed little or no primary irritation.

Mutagenic Activity

The potential antigenicity of AMSA PD was studied in guinea pigs and rabbits. In the active anaphylaxis and circulating antibodies tests, m-AMSA showed no antigenic activity. In the guinea pig maximization test, however, AMSA PD was an extreme sensitizer.

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