

Understanding Trisenox[®] (arsenic trioxide) injection



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Introduction

You have been given this booklet to learn more about a drug called Trisenox[®] (arsenic trioxide) injection. After reading this booklet you should know:

- What Trisenox[®] is
- How Trisenox[®] works
- The possible side effects of Trisenox[®]
- How Trisenox[®] is given

This booklet is meant to provide you with general information only. It is not meant to replace the advice of your doctor or nurse. Your doctor or nurse can answer questions related to your specific treatment plan. All words that appear in **bold** type are defined in the glossary at the end of the booklet.

What is Multiple Myeloma?

Multiple myeloma (also known as myeloma and as plasma cell neoplasm) is a malignancy of the **immunoglobulin- (antibody)** producing plasma cells found in the **bone marrow**. It is a hematologic malignancy resembling leukemia. However, the malignant plasma cells, or myeloma cells, rarely enter the bloodstream as in a true leukemia. Instead, the myeloma cells accumulate in the bone marrow, causing:

- Disruption of normal bone marrow function, most commonly giving rise to anemia (a low level of red blood cells in the bloodstream), although reduction in white blood cell and platelet counts can also occur

- Damage to bone surrounding accumulated myeloma cells
- Release of an abnormal protein, monoclonal protein (M protein), into the bloodstream
- Suppression of normal immune function, observed as reduced levels of normal immunoglobulins and increased susceptibility to infection

Myeloma cells can also grow in the form of localized tumors or **plasmacytomas**. Plasmacytomas may be single or multiple and either medullary (confined within bone marrow and bone) or extramedullary (outside of the bone). When there are multiple plasmacytomas inside or outside bone, this condition is also called multiple myeloma.

The Stages of Multiple Myeloma

Stage I (low cell mass): Early disease. The bone structure appears normal or close to normal on x-ray images; the number of red blood cells and amount of calcium in the blood are normal or close to normal, and the amount of M protein is very low.

Stage II (intermediate cell mass): An intermediate stage between stage I and III

Stage III (high cell mass): More advanced disease. One or more of the following are present:

- Anemia
- A high level of calcium in the blood

- More than 3 areas of advanced lytic bone lesions
- A high level of M protein in the blood or urine

Multiple myeloma is a serious malignancy, but it is treatable. Many patients experience a series of responses, relapses, and remissions. With new treatments, many patients are able to live better and longer post-diagnosis.

Following diagnosis, several options are available for initial or frontline therapy. For patients who may be candidates for high-dose therapy with transplant, various induction regimens can be considered, including Thalomid® (thalidomide) with dexamethasone, dexamethasone alone, or other dexamethasone-containing combinations. The combination of the alkylating agent melphalan plus prednisone, a simple oral therapy, is an option for patients not considering bone marrow (stem cell) transplant with intravenous high-dose melphalan. At the time of relapse, newer agents are frequently required to achieve further response. Revlimid® (lenalidomide) is an important new agent available for use in this setting. Velcade® (bortezomib) is also an important new agent available for relapsed myeloma.

What is Trisenox® and How Does it Work?

Trisenox® (arsenic trioxide) injection is a type of anticancer agent that is derived from arsenic, a naturally occurring compound that has been used for over two thousand years in Chinese and western medicine to treat a wide range of disorders. In the 1930s, naturally occurring arsenic was found to be effective for treating a type of leukemia known as chronic myelogenous leukemia (CML). More recently, interest was renewed in this agent as an anticancer agent when researchers reported promising results in patients receiving it for the treatment of acute promyelocytic leukemia (APL). In 2000, Trisenox® was approved by the U. S. Food and Drug Administration (FDA) for the treatment of APL, and researchers have continued to explore the use of Trisenox® in the treatment of other cancers of the blood. Laboratory and clinical trials continue to investigate whether Trisenox® is safe and effective in the treatment of other blood disorders including multiple myeloma. Although the exact mechanism for how Trisenox® works continues to be explored, its anticancer activity is believed to arise from multiple processes:

- Trisenox® appears to cause cancer cells to self-destruct by a natural biologic process called apoptosis. When activated, apoptosis programs cells to destroy themselves.
- In APL cells, Trisenox® may cause the leukemia cells to differentiate partially, and

become more like non-malignant blood cells. Whether Trisenox® has this particular activity in myeloma cells remains to be seen.

- Trisenox® may also prevent myeloma cells from performing another biologic process called angiogenesis (the growth of new blood vessels). As a result, cancer cells are unable to obtain nutrients for survival and growth from the bloodstream.
- Trisenox® may also inhibit the growth of myeloma cells by inhibiting molecules in the bone marrow and blood that promote cellular growth.
- Trisenox® may also disrupt the function of mitochondria, small structures within cells that provide energy, by increasing the production of reactive oxygen species.

How is Trisenox® being investigated in Multiple Myeloma?

LABORATORY STUDIES

Trisenox® is approved by the FDA for the treatment of acute promyelocytic leukemia (APL). However, it is being investigated for the treatment of multiple myeloma. Clinical trials in patients with myeloma are based on studies of Trisenox® in myeloma cell lines and cells from patients with myeloma in the laboratory. In these studies, Trisenox® inhibited the growth of these cells, induced apoptosis, and had anti-angiogenic activity.

The ability of Trisenox® to destroy cancer cells is enhanced when levels of a

compound called glutathione are lowered in cancer cells. Because ascorbic acid (more commonly known as vitamin C) has this ability, researchers have performed laboratory experiments in myeloma cells and demonstrated that Trisenox[®] activity was enhanced in combination with ascorbic acid, even in myeloma cells from patients whose disease was resistant to other chemotherapy agents. Trisenox[®] activity was also enhanced in laboratory studies in combination with dexamethasone or melphalan.

CLINICAL STUDIES OF TRISENOX[®] IN MYELOMA

All clinical studies of Trisenox[®] have been in patients with relapsed or refractory myeloma. Trisenox[®] was studied as a single agent in a Phase II trial in a small number of patients. These patients received daily doses of Trisenox[®] for 2 months. Because of limited responses and some serious side effects, another Phase II trial tested a higher, less frequent dose of Trisenox[®], administered 5 days per week for two weeks with a 2-week rest period (4-week cycle). In this small group of patients with relapsed, refractory myeloma,



the response was higher and longer lasting. A third study evaluated twice-weekly Trisenox[®] followed by a 3-week rest period at the same and higher doses. High-dose corticosteroids were added to the treatment regimen for patients whose disease progressed.

TRISENOX[®] IN COMBINATION WITH OTHER DRUGS

Because Trisenox[®] has shown activity in combination with other agents in the laboratory, several clinical studies are investigating Trisenox[®] combination therapy. These studies are summarized below.

Trisenox[®] with Ascorbic Acid (Vitamin C)

Because ascorbic acid enhanced the activity of Trisenox[®] in myeloma cells, it is being studied in patients. A Phase I/II trial evaluated two doses of Trisenox[®] plus ascorbic acid in patient with relapsed or refractory myeloma. The Phase I portion of the trial is complete and established the dose for the Phase II portion of the trial.

TAD Therapy: Trisenox[®] with Ascorbic Acid and Dexamethasone

The combination of Trisenox[®], ascorbic acid, and dexamethasone (known as TAD therapy) has been studied in various regimens in several Phase II studies. Some responses have been seen with this combination.

Trisenox[®], Ascorbic Acid, Dexamethasone, and Thalomid[®]

This combination was tested in a Phase II study. Four of 13 evaluable patients responded

and the median progression-free survival has not been reached at a median follow-up of 9.5 months. Although the regimen was well-tolerated, 3 patients had abnormal blood clotting events, including 2 with deep vein thrombosis (DVT) and one with a pulmonary embolism (PE).

Melphalan with Trisenox® and Ascorbic Acid

In 10 patients, ascorbic acid and melphalan with Trisenox® (a combination known as MAC therapy) gave encouraging results, showing that the MAC regimen is active and very well tolerated, with no serious side effects. All patients treated responded to therapy, and 6/10 (60%) patients remained disease free for prolonged period, including 2 patients responding for more than 1 year. Melphalan was discontinued after 36 weeks of treatment and patients received Trisenox® and ascorbic acid. These results have led to a larger Phase II study to further evaluate the MAC regimen with the addition of corticosteroids for progressive disease. Objective responses have been seen in 31 of 65 patients (48%) enrolled, with a median duration of response of 12 months, median overall survival of 19 months, and median progression-free survival of 7 months. A different combination of ascorbic acid and melphalan with Trisenox® (a combination known as MAT therapy) has been tested in a small number of patients.

The combination of high dose melphalan and ascorbic acid with one of two doses of Trisenox® or without Trisenox® was tested in

a Phase I/II trial of safety and efficacy as a conditioning regimen prior to autologous stem cell transplantation. There was no difference in response rates, progression-free survival, or overall survival among the three treatment groups. Treatment with Trisenox® did not delay or inhibit stem cell engraftment and was well tolerated.

Trisenox® with Velcade® and Ascorbic Acid

Three dose levels of Velcade® were tested in combination with Trisenox® and ascorbic acid. The combination was investigated in a Phase I/II trial, in which there were 6 patients responding of 22 enrolled, with more responses in the higher Velcade® dose groups.

WHAT IS NEXT FOR TRISENOX®?

Research is ongoing to evaluate Trisenox® for the treatment of myeloma. Current and future clinical trials will continue to focus on combining Trisenox® with other agents, including Velcade®, Thalomid®, melphalan, and dexamethasone. The goal of these trials is to develop new treatment regimens that improve the response of patients to therapy, maintaining or improving their quality and length of life.

In addition to being evaluated in myeloma, Trisenox® continues to be investigated in other blood disorders, including several forms of leukemia, lymphoma, and myelodysplastic syndromes, as well as solid tumor cancers such as prostate cancer and melanoma.

What are the Possible Side Effects of Trisenox®?

Generally, most of the side effects associated with Trisenox® are manageable and predictable. The most important side effects are described here. This is not a complete list of side effects. Your doctor or nurse can provide more information in greater detail about these and other possible side effects. Although much of the clinical experience with Trisenox® has been in patients with APL, over 1300 patients with multiple myeloma have been treated with Trisenox®. The side effects seen in patients with myeloma are similar to those seen in patients with APL. However, increased reports of cytopenia, or decreased numbers of cells in the blood, have been observed in patients with myeloma treated with Trisenox®.



Important Safety Information

- If you are pregnant or are planning to become pregnant, inform your doctor. Women of childbearing potential are advised to avoid pregnancy while taking Trisenox®. Laboratory studies indicate that Trisenox® is potentially harmful to developing fetuses.
- You should not take Trisenox® if you are nursing. Because arsenic may be present in excreted human milk, if you are breast-feeding, you are advised to discontinue either breast-feeding or Trisenox® therapy.
- If you have a documented hypersensitivity to arsenic or are intolerant of Trisenox® therapy, you should not take Trisenox®.

Three potentially serious side effects that have occurred in patients treated with Trisenox® are:

- APL differentiation syndrome
- Hyperleukocytosis
- QT interval prolongation

APL differentiation syndrome and hyperleukocytosis have been seen primarily in patients with APL, and may be uncommon in patients with multiple myeloma.

APL DIFFERENTIATION SYNDROME

Symptoms of APL differentiation syndrome include fever, sudden weight gain, difficult breathing, and accumulation of fluid in the lungs, heart, and chest. You may be asked to weigh yourself daily during the first few

weeks of treatment and to report right away any increases in weight, which may indicate fluid accumulation. You should inform your physician if you experience any of these symptoms. This side effect is managed by immediate treatment with high-dose corticosteroids and diuretics.

HYPERLEUKOCYTOSIS

Hyperleukocytosis is an unusual increase in the number of white blood cells. Your physician will monitor your blood to check for this side effect..

QT INTERVAL PROLONGATION

QT interval prolongation is an increase in the time it takes the heart to relax between beats. This has the potential to cause fainting or more serious side effects. Your physician will monitor you using electrocardiograms (ECGs) during treatment to detect any changes in your heart rhythm. Your blood may be tested for low levels of magnesium or potassium. Daily doses of these electrolytes



may be prescribed, since adequate levels of magnesium and potassium help prevent heart rhythm changes.

Common side effects that may arise while receiving Trisenox[®] include dizziness, light-headedness, and low blood pressure. Should these symptoms occur, the rate at which Trisenox[®] is infused may be altered.

Other, less serious side effects that may occur while receiving Trisenox[®] include:

- Increased white cell counts
- Nausea, vomiting, diarrhea, or abdominal pain
- Fatigue
- Fluid retention (swelling)
- Hyperglycemia (abnormally increased blood sugar levels)
- Shortness of breath
- Cough
- Rash or itching
- Headaches
- Dizziness

Notify your doctor or nurse if you experience any of the above symptoms.

Will Taking Other Drugs or Medications Affect Trisenox[®]?

Inform your doctor of any other prescription or over-the-counter medications, vitamins, diet supplements, or herbal products you are taking, as these or other compounds may interact or interfere with Trisenox[®] treatment.

This is particularly important if you take heart medications or other medications that may affect your heartbeat, as these drugs may adversely interact with Trisenox[®] and increase the risk of potentially harmful irregular heartbeats.

How is Trisenox[®] Given?

Trisenox[®] is given by intravenous (I.V.) infusion over one to two hours. If low blood pressure, light-headedness, or dizziness occurs when Trisenox[®] is first given, administration may be slowed down and extended over a four-hour period to alleviate these symptoms. In almost all cases, Trisenox[®] can be given on an outpatient basis.

What is the Dose and Schedule for Trisenox[®]?

The most effective dose and schedule for treating multiple myeloma with Trisenox[®] is still being determined in clinical trials, as are the types and doses of other agents that may be administered with Trisenox[®].

How Can I Receive Treatment with Trisenox[®]?

At present, Trisenox[®] is available to patients with multiple myeloma and other types of cancer (other than APL) who are willing to participate in clinical trials. For more information on how to enroll in a clinical trial, contact the IMF.

What Questions Should I Ask My Healthcare Provider about Trisenox[®]?

Questions you may want to ask your doctor or healthcare professional before receiving Trisenox[®] include:

- How often and how long will I be taking Trisenox[®]?
- What side effects may occur while I am receiving Trisenox[®]?
- Will Trisenox[®] affect my daily life?
- Will Trisenox[®] interfere with my other medications?
- Is there anything I should avoid while taking Trisenox[®]?
- Can you provide me with additional patient education information about Trisenox[®]?

Where Can I Get More Information?

Contact the International Myeloma Foundation (IMF) for additional information about multiple myeloma and approved therapies. Your doctor or healthcare provider may have written information available regarding Trisenox[®]. Additional information can be obtained by visiting the Cephalon Oncology Inc., website at www.CephalonOncology.com and www.TRISENOX.com.

IMF hotline:

USA & Canada only: 800-452-CURE (2873)

Elsewhere: 818-487-7455

IMF Web site: www.myeloma.org

About the IMF

*“One person can make a difference,
Two can make a miracle.”*

Brian D. Novis
IMF Founder

Myeloma is a little-known, complex, and often misdiagnosed bone marrow cancer that attacks and destroys bone. Myeloma affects approximately 75,000 to 100,000 people in the United States, with approximately 20,000 new cases diagnosed each year. While there is presently no known cure for myeloma, doctors have many approaches to help myeloma patients live better and longer.

The International Myeloma Foundation (IMF) was founded in 1990 by Brian and Susie Novis shortly after Brian’s myeloma diagnosis at the age of 33. It was Brian’s dream that future patients would have easy access to medical information and emotional support throughout their battle with myeloma. He established the IMF with the 3 goals of treatment, education, and research. He sought to provide a broad spectrum of services for patients, their families, friends, and health care providers. Although Brian died 4 years after his initial diagnosis, his dream didn’t. Today the IMF reaches out to an international membership of more than 150,000. The IMF was the first organization dedicated solely to myeloma, and today it remains the largest.

The IMF provides programs and services to aid in the research, diagnosis, treatment, and management of myeloma. The IMF ensures that no one must brave the myeloma battle alone.

We care for patients today, while working toward tomorrow’s cure.

How Can the IMF Help You?

PATIENT EDUCATION

INFORMATION PACKAGE

Our free IMF InfoPack provides comprehensive information about myeloma, treatment options, disease management, and IMF services. It includes our acclaimed Patient Handbook.

INTERNET ACCESS

Log on to www.myeloma.org for 24-hour access to information about myeloma, the IMF, education, and support programs.

ONLINE MYELOMA FORUM

Join the IMF Internet Discussion Group at www.myeloma.org/listserve.html to share your thoughts and experiences.

MYELOMA MINUTE

Subscribe to this free weekly email newsletter for up-to-the-minute information about myeloma.

PATIENT & FAMILY SEMINARS

Meet with leading experts in myeloma treatment to learn more about recent advances in therapy and research.

MYELOMA MATRIX

On our website and in print, this document is a comprehensive guide to drugs in development for myeloma.

MYELOMA TODAY NEWSLETTER

Our quarterly newsletter is available free of charge by subscription.

SUPPORT

MYELOMA HOTLINE: 800-452-CURE (2873)

Toll-free throughout the United States and Canada, the IMF Hotline is staffed by trained information specialists and is in frequent interaction with members of our Scientific Advisory Board.

SUPPORT GROUPS

A worldwide network of more than 100 myeloma support groups; these groups hold regular meetings for members of the myeloma community. The IMF conducts annual retreats for myeloma support group leaders.

RESEARCH

BANK ON A CURE®

This DNA bank will provide genetic data research for new drug development.

THE INTERNATIONAL STAGING SYSTEM (ISS)

This updated staging system for myeloma enhances physicians' ability to select the most appropriate treatment for each patient.

RESEARCH GRANTS

Leading the world in collaborative research and achieving extraordinary results, the IMF Grant Program supports both junior and senior researchers working on a broad spectrum of projects. The IMF has attracted many young investigators into the field of myeloma; they have remained in the field; and are actively pursuing a cure for this disease.

Glossary

Acute promyelocytic leukemia (APL): A subtype of the cancer known as acute myeloid leukemia (AML). APL is characterized by abnormal promyelocytes, a type of white blood cell. When APL occurs, these abnormal promyelocytes accumulate in the bone marrow and peripheral blood and replace normal blood cells.

Alkylating agent: A chemotherapy agent that prevents the growth and division of new cancer cells by inhibiting their ability to replicate DNA.

Anemia: A low level of red blood cells in the bloodstream.

Angiogenesis: The growth and formation of new blood vessels, often stimulated by cancer cells to obtain nutrients.

Anti-angiogenic activity: Ability to inhibit new blood vessel development.

Antibody: A protein produced by some of the body's white blood cells that helps fight infection.

APL differentiation syndrome: A potentially serious side effect of which is characterized by fever, sudden weight gain, difficult breathing, and fluid accumulation.

Apoptosis: The programmed death of cells through biologic processes. Although it occurs naturally and normally in several biologic functions, apoptosis can be stimulated in tumor cells by certain cancer drugs.

Ascorbic acid: Vitamin C; required for healthy teeth and gums, helps in the absorption of iron, aids in the maintenance of normal connective tissue, and promotes wound healing. It also is an antioxidant that contributes to a healthy immune system. It is being tested in some clinical trials in combination with Trisenox®.

Bone marrow: A soft, spongy tissue found in most large bones that produces red and white blood cells and platelets.

Chemotherapy: Use of chemicals to treat or control cancer.

Chronic myelogenous leukemia (CML): A slowly progressing blood disorder in which too many white blood cells are made in the bone marrow, eventually replacing normal white blood cells.

Corticosteroids: A group of steroid hormones that includes dexamethasone; used to treat myeloma and other cancers, as well as problems arising from treatment.

Cytopenia: Abnormally decreased numbers of blood cells.

Dexamethasone: A synthetic steroid similar to steroid hormones produced naturally in the adrenal gland. Dexamethasone is used to treat leukemia, lymphoma, and certain problems caused by other cancers and their treatment.

Differentiation: Process by which cells become more mature and less likely to continue to divide.

Diuretics: Drugs that rid the body of excess fluid.

Deep vein thrombosis (DVT): Blood clot that originates in deep veins, usually in the pelvis or legs, that may move to other areas of the body, sometimes with fatal consequences.

Electrocardiogram (ECG): A test used to evaluate heart rhythm, in which electric conductors are placed on the body to produce an electrical reading of the heart's contractions.

Electrolytes: Various chemicals in the blood including magnesium and potassium.

Hyperglycemia: Abnormally increased blood sugar levels.

Hyperleukocytosis: Abnormally increased levels of white blood cells.

Immune system: The system of white blood cells and their products that helps the body resist infection and some cancers.

Immunoglobulin: An antibody.

Intravenous (I.V.) infusion: Delivery of a drug or fluid into the body using a needle inserted into a vein.

Leukemia: Cancer arising from one of the blood-forming cells in the bone marrow.

Lymphoma: Cancer arising from certain cells of the immune system.

Lysis (lytic): Dissolution or destruction of cells.

Malignant: Cancerous.

Melphalan: An anticancer drug that belongs to a class of drugs called alkylating agents. Alkylating agents work by damaging DNA and inducing the death of tumor cells.

Mitochondria: Small structures within cells that provide energy.

Monoclonal protein (M protein): An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. A high level of M protein indicates that myeloma cells are present in large numbers.

Multiple myeloma: A cancer arising from the plasma cells in the bone marrow. The plasma cells in patients with multiple myeloma form abnormal antibodies, possibly damaging the bone, bone marrow, and other organs.

Myelodysplastic syndromes (MDS): A group of bone marrow neoplastic diseases in which not enough healthy blood cells are produced. MDS have some features of acute myeloid leukemias.

Neoplasm: Cancer.

Plasma cell: A type of white blood cell that produces antibodies.

Plasmacytoma: A tumor made up of cancerous plasma cells.

Platelet: An element in the blood that helps with clotting, which in turn helps repair damaged blood vessels.

Pulmonary embolism (PE): Blood clot from another part of the body that is transported to the lungs in the blood, and may be fatal.

QT interval prolongation: An increase in the amount of time it takes the heart to relax in between beats.

Red blood cell: A blood cell that carries oxygen from the lungs throughout the body.

Side effect: An effect caused by treatment with a drug. The term usually refers to an unwanted effect, but some side effects may be beneficial.

Stage I (low cell mass): Early myeloma disease.

Stage II (intermediate cell mass): Stage of myeloma disease intermediate between stages I and III.

Stage III (high cell mass): More advanced myeloma disease.

Trisenox® (arsenic trioxide): An anticancer drug that is used in the treatment of several types of leukemia and other types of cancer. A derivative of naturally occurring arsenic, Trisenox® can reduce or eliminate cancer cells from patients through several mechanisms.

White blood cell: A cell made by the bone marrow that helps fight infection and/or disease.