



# **Frequently Asked Questions about Avemar**

## **1. What is Avemar®?**

Avemar is the trade-name of a standardized, natural nutrient compound that has been extensively studied for its anti-cancer and immune supporting effects. It is made by fermenting wheat germ (*Triticum vulgare*) by bakers yeast, (*Saccharomyces cerevisiae*), through a patented process (U.S. patent number 6,355,474), standardized to yield 0.4 mg/kg of the naturally occurring flavone 2,6-dimethoxy-p-benzoquinone (2,6-DMBQ) present in wheat germ.

In Hungary, where it was developed and where it is manufactured, it is classified as a "Dietary food for special medical purposes, for cancer patients," and is a standard therapy for patients with cancer. It is available in several other countries as a food, medical food, or dietary supplement including Austria, Australia, Switzerland, Italy, Slovakia, Czech Republic, Russia, Israel, and South Korea.

Sometimes referred to by the code name "MSC," Avemar has been the subject of more than 100 published reports of in vitro, in vivo and human research, including more than 20 peer-reviewed publications, most accessible by Medline, showing antitumor and immune modulating effects. These have involved extensive toxicity and safety testing and in the opinion of the expert panel assembled to ascertain the GRAS (Generally Recognised As Safe) status of Avemar, "it has the toxicological profile of bread."

## **2. Where does Avemar come from?**

Avemar is manufactured by BiroPharma of Budapest, Hungary under several quality assurance systems, including HACCP and GMP, and has been assessed and registered as meeting the ISO 9001:2000 standard and the standards for GMP production of pharmaceuticals by the National Institute of Pharmacy, Ministry of Health, Hungary.

## **3. What does Avemar do?**

Avemar is a truly remarkable natural compound that enhances the usefulness of commonly used conventional and alternative (natural and nutritional) therapy choices.

Research studies show once daily use of Avemar supports mechanisms of cellular metabolism and immune function that maintain good health with particular benefit to people with autoimmune disease and many types of cancer.

In studies of animals and humans, use of Avemar prevented development of cancerous and pre-cancerous lesions (melanoma, pancreatic, colon and oral cancers, and others), reduced the incidence and number of metastatic cancers, improved quality of life by

many measures and lengthened the time to cancer progression following surgery, radiation and chemotherapy.

Cell line, animal and human studies looking at simultaneous use with many varieties of standard chemotherapy agents, showed that Avemar didn't interfere with any of the agents, but did enhance their effects, particularly with regard to tumor metastasis. Avemar did however reduce the frequency and severity of many common side effects including nausea, fatigue, weight loss and immune suppression.

In studies specifically looking at immune effects, Avemar was shown to speed the recovery of immune function following radiation and chemo, inhibit immune suppression, improve Natural Killer (NK) cell recognition of target cells, enhance immune system regulation and increase the invasive potential of white blood cells, helping them cross through blood vessel walls and into tumors.

Results of human studies (the most studies have been conducted in patients with colorectal cancer and melanoma, but also in patients with breast, lung, colon, head and neck, oral, and pediatric cancers and patients with autoimmune disorders), supported by research in rats, mice and in vitro predict that Avemar will provide specific benefits in terms of:

- 1) Preventing the development of cancerous and precancerous lesions.
- 2) Reducing the incidence and overall number of metastatic cancers.
- 3) Lengthening the time to cancer recurrence following surgery, radiation and chemotherapy.
- 4) Enhancing and not interfering with the anticancer effects of chemotherapies.
- 5) Enhancing the quality of life, physical condition and performance of late stage and other cancer patients.
- 6) Decreasing the severity of the immune suppressive effects of surgery, radiation and chemotherapy anticancer therapies.
- 7) Expanding the applicability of anticancer therapies by preventing immunosuppressive side-effects.
- 8) Speeding the recovery of normal immune functions following immunosuppressive therapies.
- 9) Preventing opportunistic infection and sepsis.
- 10) Preventing cancer related cachexia.

- 11) Reducing fatigue in late stage cancer patients.
- 12) Preventing cancer cell proliferation.
- 13) Inhibiting cancer cell motility.
- 14) Stimulating cancer cell apoptosis.
- 15) Enhancing the ability of NK cells to identify and kill cancerous and other target cells by down regulating the presentation of MHC-I molecules on infected cells.
- 16) Stimulating the production of TNF-alpha by macrophages.
- 17) Enhancing the tumor invasive potential of immune system cells by up regulating ICAM-A molecules in microvascular endothelial cells.
- 18) Up regulating Th1 (cellular) immune function, while inhibiting Th2 (humoral) immune function.
- 19) Reducing inflammation and symptoms of Rheumatoid arthritis, systemic lupus erythematosus (SLE) and other autoimmune diseases associated with the predominance of Th2 over Th1 immune response.

#### **4. What research supports the use of Avemar?**

Abstracts of research on Avemar that demonstrate its beneficial effects can be found on the at the National Institutes of Health, National Library of Medicine website, Medline (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) by using the search terms Avemar and “fermented wheat germ.” Full text of most of the English language, peer-reviewed publications can be found at the website, [www.avemarrsearch.com](http://www.avemarrsearch.com).

In terms of anti-cancer benefits, the most impressive research was published in the *British Journal of Cancer*, 2003, a controlled study of 170 subjects with primary colorectal cancer, where approximately half the patients were treated with “standard of care” (surgery, radiation, chemo and other appropriate therapy) only, and the other half was treated with “standard of care” plus Avemar. Results showed an impressive advantage by adding Avemar to “standard of care” --

82% reduction in new recurrences (p <.01)  
67% reduction in metastasis (p <.01)  
62% reduction in deaths (p <.01)

In terms of immune supportive benefits, the most impressive research was published in the journal *Pediatric Hematology Oncology* in 2004. In a controlled study with 22 children undergoing cancer therapy for solid tumors, it was found that Avemar helped to

prevent the chemotherapy induced suppression of immune function that often leads to the development of life threatening opportunistic infections. Children in the treatment and control groups were matched by diagnosis, histopathology, clinical stage, gender, treatment schedule, and age. Concurrent use of Avemar was shown to reduce incidents of febrile neutropenia (episodes of low white blood count and high fever) that are the hallmarks of immune suppression and the onset of opportunistic infections by 43%.

Most of the Avemar published research is very technical, but worth reviewing. As a body the research is impressive because it is published in very well regarded peer-review journals, the research is recent, involving many groups of scientists, and showing a methodical progression from cell line (*in vitro*) and animal (*in vivo*) research to human clinical trials.

## **5. How does Avemar work?**

Avemar has been shown to have many mechanisms of action, not surprising since as a natural compound, it is composed of a naturally occurring blend of many medicinally active constituents.

### ***Selectively inhibiting glucose metabolism in cancer cells.***

The marker compound for which it is standardized in manufacturing, *2,6-dimethoxy-p-benzoquinone* (2,6-DMBQ) and related *methoxy-substituted benzoquinones*, are suggested to provide Avemar's most unique benefit of inhibiting non-oxidative metabolism of glucose (anaerobic glycolysis) by cancer cells. Dr. Albert Szent-Györgyi, recipient of the Nobel Prize in Medicine for his part in the discovery of vitamin C and for determining the processes of cell metabolism, theorized 2,6-DMBQ and related *methoxy-substituted benzoquinones* provided in supplemental quantities would help to chaperone the cellular metabolism, and help prevent states of hyper metabolism characteristic of cancer cells.

Cancer cells utilize glucose at a 10 to 50 times higher rate than normal cells through the pathway of non-oxidative metabolism, a phenomenon known as the "Warburg effect." Although this method of metabolism is very inefficient in the production of ATP compared with the healthy, oxidative metabolism (aerobic glycolysis) it is very efficient at the utilization of carbon atoms from glucose for the production of RNA and DNA – fueling the rapacious growth and spread of tumors.

Studies conducted by Dr. Szent-Györgyi and published in the Proceedings of the National Academy of Sciences USA in the 1960's with naturally occurring and synthetic DMBQ showed effects against cancer cell lines, confirming his theory. But at the time, the concept of cytotoxic cancer therapies was becoming the dominant theory in cancer treatment, and so this mechanism of cytostatic therapy was unappreciated.

Recently, research by Boros and colleagues at UCLA with Avemar have shown it selectively inhibited glucose metabolism in healthy cells (*strictly speaking Boros shows that it disrupts glucose 6-phosphate dehydrogenase (G6PDH) and transketolase enzyme*

*function in the glycolysis/pentose cycle*), dramatically reducing glucose utilization in a broad range of cancer cell types, the more malignant the cell line, the greater its rate of glucose utilization, the more dramatic Avemar's inhibitory effect. These studies also showed that a 50 times higher concentration of Avemar was needed to inhibit glucose utilization in normal healthy cells, implying a very broad "therapeutic index" which describes the spread between the beneficial dose of a medicinal compound and its harmful dose (the broader the therapeutic index for a treatment, the safer it is).

The Boros research showed that Avemar's inhibition of non-oxidative glucose metabolism corresponded with a reduction in the synthesis of RNA and DNA associated with the proliferation of cancer cells and the growth and spread of tumors, and an increase in RNA and DNA synthesis associated with healthy functions of cellular differentiation and repair.

By starving cancer cells of the glucose metabolism they need, Avemar helped cancer cells behave less like cancer cells and more like normal cells. Animal and human studies have borne this out, showing that Avemar is most effective on metastatic tumors, typically faster growing than primary tumors, and most likely to be responsible for cancer related mortality.

### ***Assisting mechanisms of apoptosis, programmed cell death***

Most radiation, chemotherapy and herbal therapies that kill cancer cells, work by inducing programmed cell death (cell suicide) a process called apoptosis. Avemar has been shown to enhance the effectiveness of therapies that induce programmed cell death by reducing the synthesis, by reducing the production of one enzyme called *PARP* that cancer cells over produce, and increasing the production of another called *Caspase-3* that cancer cells under produce.

PARP (poly-ADP-ribose) is an enzyme that repairs breaks in DNA prior to cell division. Cancer cells need a lot of PARP because they reproduce so chaotically, the process of DNA replication introduces a lot of breaks and other mistakes, and because they are reproducing so quickly. Without adequate PARP, cancer cells cannot complete DNA replication.

Caspase-3 is an enzyme, that in the absence of PARP and the presence of many DNA breaks, induces the processes of programmed cell death. When used in combination with other therapies that induce apoptosis by other mechanisms, Avemar lowers the "threshold of apoptosis" making them more effective.

### ***Unmasking the Enemy***

Cancer cells evade the immune system's first line of defense, Natural Killer (NK) cells, by displaying a false cell membrane feature called MHC-1 (Major Histocompatibility Complex 1), that essentially says "don't attack me, I am one of the good guys." Avemar

has been shown to reduce the display of MHC-1 in cancer cell lines, resulting in improved NK cell recognition of tumors, and increased cell targeting and death.

### ***Helping to enhance the immune system coordinated functioning***

There are many aspects to the immune system's response to cancer cells and tumors, and Avemar has been shown to improve how well these various elements work together.

Broadly speaking, Avemar has been shown to modulate the balance between Th1 and Th2 cytokines, chemical messengers of the immune system that correspond with the two compartments of immune function – *cellular immunity* (regulated by Th1 cytokines), which refers to the specific action of white blood cells against specific target cells, and *humoral immunity* (regulated by Th2 cytokines), which refers to soluble factors, hormones, cytokines, neurotransmitters, anti-bodies and other compounds that are dissolved in the tissues and blood stream that make the body a hostile environment for pathogens, or that help the body recover from injury.

Many people with cancer and other chronic illnesses have low cellular immunity, (low levels of Th1 cytokines) because of various causes, and as a result have elevated humoral immunity (high Th2 cytokines). But, many of the factors that help the body recover from injuries, that enhance the proliferation of endothelial, white blood and other cell types, also fuels the proliferation of cancer cells. Avemar has been shown to reduce the production of Th2 cytokines, and restore the normal balance of immune function, increasing immune regulation.

One aspect of this, as explained above, is that NK cell targeting and killing activity against cancer cells is enhanced. Other research shows that Avemar enhances the appropriate production of Tumor Necrosis Factor(TNF)-alpha by macrophages, a cytokine that targets and kills cancer cells. It has also been shown to upregulate the production of the cytokine, ICAM-1 (Inter Cellular Adhesion Molecule 1), that enables macrophages and T-cells to slip through blood vessel walls which enhances their tumor invasive properties.

### **6. How is Avemar used?**

Avemar is available as a dietary supplement in an instant drink mix format. It combines Avemar with natural orange flavoring and fructose, in pre-measured packets providing 8.5 g of Avemar, the recommended daily usage, intended to be mixed with 8 oz. of cold water or any other beverage providing less than 10 mg of vitamin C.

### **7. What is the recommended usage of Avemar ?**

As a dietary supplement, recommended usage is one Avemar packet per day, mixed with 8 oz (240 ml) cold water (or any other beverage containing less than 10 mg of vitamin C). Mixing is best accomplished by shaking in a closed container (*add liquid first, then Avemar, close lid and shake*). It is best to consume within 30 minutes of mixing.

Avemar should be consumed one hour before or after a meal, and two hours before or after any drugs or other dietary supplements. For best results use Avemar daily.

For people over 200 lbs, the recommendation is to use two packets per day, for people under 100 lbs, the recommendation is to use 1/2 packet per day. Consult with a healthcare professional for recommended usage levels for children, and for guidance on alternative usage levels, and use in combination with other dietary supplements.

#### **8. Who should not consume Avemar ?**

Women who are pregnant or nursing should not consume Avemar. It should not be consumed by people who have had an organ or tissue transplant, for those suffering from bleeding GI ulcers, malabsorption syndrome, gluten sensitive enteropathies (celiac sprue), fructose intolerance or who have hypersensitivity to gluten, wheat germ or any of the components or ingredients of this product.

It is recommended to discontinue Avemar usage 2 days before barium X-ray contrast examinations and resume 2 days after the completion of the examination.

**Allergen Statement: Avemar contains wheat ingredients.** Although the process of making the product removes all gluten, the principle allergen in wheat, the product comes in contact with gluten containing wheat, and the possibility of contamination exists.

#### **9. How long does someone have to be on this before they notice a difference?**

People often report improvements in appetite, energy and daily activity within 3 weeks of beginning to take Avemar daily. Objective measures in terms of blood markers, CAT scans, MRI's etc, typically occur within 3 months.

#### **10. How long should someone continue to take Avemar?**

For long-term results, one should use Avemar for at least 6 months. Human clinical trials involving hundreds of subjects taking Avemar daily over a period of several years have proven it safe and beneficial for long-term use. Since Avemar supports the basic mechanisms that the body utilizes to respond to stress and the daily challenges to health, it may make sense to use it continuously.

#### **11. Is there a recommendation for using Avemar at a lower “maintenance level” of use?**

Since research has shown very dramatic and unique benefits from using Avemar at the suggested level of use, and since this level of use is entirely safe and non-toxic, research has not considered the use of Avemar at lower levels. Consultation with a physician may help determine whether a lower “maintenance level” of Avemar use is appropriate.

## **12. Can Avemar be used as a preventative?**

Research in animals has shown that Avemar will reduce the rate of cancer initiation.

## **13. What other reasons would someone take this product besides having cancer?**

Because many auto-immune disorders are caused by an imbalance in Th1/Th2 levels, Avemar has demonstrated an effective use in clinical studies involving Lupus and Rheumatoid arthritis patients. For instance, a study published in the medical journal *Lupus*, showed that “**AVEMAR (a new benzoquinone-containing natural product) administration interferes with the Th2 response in experimental Lupus and promotes amelioration of the disease,**” and a study presented at the 2004 Auto-Immune Conference in Budapest Hungary showed that “**Oral treatment with 2 x 1.0 or 2 x 2.5 g/kg/day Avemar significantly inhibited the development of secondary (immune mediated) response in Rheumatoid Arthritis. Avemar exerted an inhibitory effect on Rheumatoid Arthritis comparable with that of dexamethasone (2 x 0.05 mg/kg/day) and indomethacin (2 x 0.5 mg/kg/day).**”

## **14. If someone skips a dose of Avemar, will it still work?**

The effects of Avemar do not immediately dissipate if one dose is skipped. However, since its effects are gradual and continual, skipping doses is not recommended and should be avoided to get Avemar's full effect.

## **15. How do I store Avemar ?**

Avemar can be stored at room temperature, but it should not be stored at temperatures above 80 Fahrenheit. Each packet is sealed, so humidity should not be a problem.

## **16. Is Avemar organic?**

Avemar is 100% natural, made from wheat germ extract fermented by bakers yeast. It is not “certified organic,” but it is free of chemicals and synthetics.

## **17. Are there any side effects from using Avemar?**

In the first few days of using Avemar, some people have reported uneasiness in their stomachs. However, these feelings went away after a few days and no vomiting, diarrhea or any other GI symptom was reported. Also, there were very few “adverse events” reported in all of the clinical studies done on Avemar and almost all of those reported adverse events were related to an earlier version of Avemar. Essentially, only very minor GI discomfort from Avemar use has been reported.

### **18. Can it be taken during radiotherapy or chemotherapy?**

Extensive research, cell line, animal and human data, have shown that Avemar does not interfere with the mechanisms of most cancer therapies, but rather enhances their beneficial effects, while reducing side effects.

### **19. How does it compare to other wheat germ supplements?**

There is really no comparison. Pure wheat germ, wheat germ oil, and wheat germ extract powder (often found as an ingredient in “green drinks”) may have generally beneficial properties, but research on these products has not shown the effects that Avemar has demonstrated on helping to maintain normal, health cellular metabolism and immune regulation (see research on Avemar for additional information, [www.avemarrsearch.com](http://www.avemarrsearch.com)).

### **20. Can Avemar be used with other dietary supplements?**

There are many dietary supplements, and special diets that may benefit people who may wish to use Avemar. None of them will interfere with Avemar, and Avemar will not interfere with them, as long as other supplements are consumed two hours before, or two hours after taking Avemar. Consult with a health care professional that specializes in natural and nutritional medicine for a comprehensive protocol of diet, exercise and dietary supplements.

### **21. Can Avemar be used in along with prescription medications?**

Avemar has been subjected to hundreds of studies resulting in more than 20 peer-reviewed publications, including studies that look at potential drug interactions. An answer as to whether Avemar will interact with a specific drug is best obtained by consulting with a pharmacist or physician.

Pharmacists and doctors can find research that can answer most questions on interactions at the website, [www.avemarrsearch.com](http://www.avemarrsearch.com).