



BlueCross BlueShield
of Alabama

Name of Blue Advantage Policy:
Antineoplaston Cancer Therapy

Policy #: 280

Latest Review Date: September 2022

Category: Medicine

BACKGROUND:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
 - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - *Furnished in a setting appropriate to the patient's medical needs and condition;*
 - *Ordered and furnished by qualified personnel;*
 - *One that meets, but does not exceed, the patient's medical need; and*
 - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **antineoplaston therapy**, including, but not limited to, antineoplaston A10 and AS2-1, as a **non-covered** benefit and as **investigational** for all conditions, including, but not limited to any malignancy and HIV infection.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Antineoplastons are a group of medium and small size synthetic peptides and amino acid derivatives that are thought to be components of a biochemical defense system that functions by inducing differentiation in neoplastic cells. Two main groups of antineoplastons have been isolated. One includes compounds with broad spectrum activity in many different cell lines and the other includes compounds with a narrow spectrum of activity against single cell lines. Five of the broad spectrum antineoplastons have been isolated from normal human urine: A1, A2, A3, A4, and A5. Antineoplaston A10 was the first active ingredient that has been reproduced synthetically. Antineoplaston AS2-1 and AS2-5 are metabolites of antineoplaston A10 that have also been synthesized. Antineoplastons A10 and AS2-1 have been most commonly researched as a treatment of a wide variety of malignancies and HIV infections.

Sodium phenylbutyrate (Buphenyl) taken orally is metabolized in the liver into a combination of phenylacetylglutamine and phenylacetate, which then enter the bloodstream. These two chemicals are the prime ingredients of antineoplaston AS2-1.

KEY POINTS:

Summary of Evidence

Antineoplastons are a group of synthetic compounds that were originally isolated from human blood and urine by Stanislaw Burzynski, M.D., Ph.D. in Houston, Texas. Dr. Burzynski has used antineoplastons to treat patients with a variety of cancers. In 1991, the National Cancer Institute (NCI) conducted a review to evaluate the clinical responses in a group of patients treated with antineoplastons at the Burzynski Research Institute in Houston.

The medical records of seven brain tumor patients who were thought to have benefitted from treatment with antineoplastons were reviewed by NCI. This did not constitute a clinical trial but, rather, was a retrospective review of medical records, called a “best case series”. The reviewers of this series found evidence of antitumor activity and NCI proposed that formal clinical trials be

conducted to further evaluate the response rate and toxicity of antineoplastons in adults with advanced brain tumors.

Investigators at several cancer centers developed protocols for two phase II clinical trials with review and input from NCI and Dr. Burzynski. These NCI-sponsored studies began in 1993 at the Memorial Sloan-Kettering Cancer Center, the Mayo Clinic, and the Warren Grant Magnuson Clinical Center at the National Institutes of Health. Patient enrollment in these studies was slow, and by August 1995, only 9 patients had entered the trials. Attempts to reach a consensus on proposed changes to increase accrual could not be reached by Dr. Burzynski, NCI Staff, and investigators. On August 18, 1995, the studies were closed prior to completion. Because of the small number of patients in these trials, the NCI concluded that no definitive conclusions can be drawn about the effectiveness of treatment with antineoplastons.

At present, the Burzynski Research Institute is conducting trials using antineoplastons for a variety of cancers. Information about these trials is available from the Cancer Information Service or the NCI's web site: <http://www.cancer.gov> or http://www.cancer.gov/clinical_trials.

A recent search of the literature identified some case reports, case series, and data from single institution phase II trials. Dr. Burzynski is the author of many of these reports. Two of the more recently published reports are summarized below.

In a Phase II clinical trial, Burzynski, et al (2005), studied the effect of antineoplaston (ANP) therapy in 13 children with primitive neuroectodermal tumors (PNETs) (median age 5 7/12 years, range 1-11 years) with either recurrent disease or high risk. The diagnoses included medulloblastoma (n = 8), pineoblastoma (n = 3), and other PNET (n = 2). Prior therapies included surgery (n = 12), chemotherapy (n = 6), or radiation therapy (n = 6). Six patients had not received chemotherapy or radiation. The treatment consisted of IV infusions of 2 formulations of ANP, A10 and AS2-1, for an average of 20 months. The results showed complete response in 23%, partial response in 8%, stable disease in 31%, and progressive disease in 38%. Six patients (46%) survived more than 5 years from the initiation of ANP; 5 were not treated earlier with radiation therapy or chemotherapy. The serious side effects included single occurrences of fever, granulocytopenia, and anemia. The study is ongoing and accruing additional patients. The authors noted that the percentage of patients' response is lower than for standard treatment of favorable PNET, but long-term survival in poor-risk cases and reduced toxicity makes ANP therapy promising for very young children, patients at high risk of complication of standard therapy, and patients with recurrent tumors.

In another published report, Burzynski, et al (2006), reported on 18 patients with brainstem glioma (4 with glioblastoma, 14 with anaplastic high-grade pathology) treated with antineoplastons in 4 phase 2 trials. Patients were treated with IV ANP (A10 and AS2-1) for a median duration of 5 months. The results showed overall survival was 39% at 2 years and 22% at 5 years. Complete response was achieved in 11%, partial response in 11%, stable disease in 39%, and progressive disease in 39% of patients. The authors concluded that ANP did contribute to survival in these patients, but this was a small study group.

In a randomized phase II study, Ogata, et al (2015), sixty-five patients with metastatic colon adenocarcinoma in the liver (underwent hepatectomy, and/or thermal ablation for liver metastasis) randomly received systemic antineoplastons plus HAI (AN arm) or HAI alone (control arm). The findings indicated that overall survival was not improved statistically in the AN arm. The recurrence of cancer was more frequent in a single organ than it was in multiple organs in the AN arm versus the control arm.

Antineoplaston therapy is not FDA approved for any indication, and there are no controlled, peer-reviewed clinical trials to validate the effectiveness of antineoplaston therapy for any indication. In summary, there is inadequate published data to permit scientific conclusions regarding the efficacy of antineoplaston therapy.

KEY WORDS:

Antineoplaston cancer therapy, antineoplastons (ANP), A10, AS2-1

APPROVED BY GOVERNING BODIES:

Sodium phenylbutyrate was FDA approved April 30, 1996 for the treatment of urea cycle disorders.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes: There are no specific codes to identify this treatment

REFERENCES:

1. Badria F, et al. Immune modulatory potentials of antineoplaston A-10 in breast cancer patients. *Cancer Letters*, August 2000; 157(1): 57-63.
2. Badria F, et al. Potential utility of antineoplaston A-10 levels in breast cancer. *Cancer Letters*, July 2000; 155(1): 67-70.
3. Buckner JC, et al. Phase II study of antineoplastons A-10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma. *Mayo Clinic Proceedings*, February 1999; 74(2): 137-145.
4. Buphenyl® (sodium phenylbutyrate). Patient packet insert.

5. Burzynski SR, et al. Long term survival and complete response of a patient with recurrent diffuse intrinsic brain stem glioblastoma multiforme. *Integrative Cancer Therapies*, September 2004; 3(3): 257-261.
6. Burzynski SR, et al. Long-term survival of high-risk pediatric patients with primitive neuroectodermal tumors treated with antineoplastons A10 and AS2-1. *Integrative Cancer Therapies*, June 2005; 4(2): 168-177.
7. Burzynski SR, et al. Phase II study of antineoplaston A10 and AS2-1 in patients with recurrent diffuse intrinsic brain stem glioma: A preliminary report. *Drugs RD* 2003; 4(2): 91-101.
8. Burzynski SR, et al. Targeted therapy with antineoplastons A10 and AS2-1 of high-grade recurrent, and progressive brainstem glioma. *Integrative Cancer Therapies* 2006; 5(1): 40-47.
9. Burzynski SR. Efficacy of antineoplastons A-10 and AS2-1. *Mayo Clinic Proceedings*, June 1999; 74(6): 641-642.
10. Burzynski SR. The present state of antineoplaston research (1). *Integrative Cancer Therapies* 2004; 3(1): 47-58.
11. Cudkowicz ME, Andres PL, et al. Phase 2 study of sodium phenylbutyrate in ALS. *Amyotroph Lateral Scier*, April 2009; 10(2): 99-106.
12. Fujii T, Yokoyama G, Takahashi H, et al. Preclinical studies of molecular-targeting diagnostic and therapeutic strategies against breast cancer. *Breast Cancer* 2008; 15(1): 73-78.
13. Fujii T. Antineoplaston induces G(1) arrest by PKCalpha and MAPK pathway in SKBR-3 breast cancer cells. *Oncology Report* 2005; 14(2): 489-494.
14. Green S. Antineoplastons. An unproved cancer therapy. *JAMA*, June 1992; 267(21): 2924-2928.
15. Hammer MR, et al. Managing social conflict in complementary and alternative medicine research: The case of antineoplastons. *Integrative Cancer Therapies*, March 2004; 3(1): 59-65.
16. Hines P, Dover GJ and Resar LM. Pulsed-dosing with oral sodium phenylbutyrate increases hemoglobin F in a patient with sickle cell anemia. *Pediatr Blood Cancer*, February 2008; 50(2): 357-359.
17. Lin J, Gilbert J, Rudek MA, et al. A phase I dose-finding study of 5-azacytidine in combination with sodium phenylbutyrate in patients with refractory solid tumors. *Clin Cancer Res*, October 2009; 15(19): 6241-6249.
18. Ogata Y, et al. Long-term survival following treatment with antineoplastons for colon cancer with unresectable multiple liver metastases: Report of a case. *Surgery Today* 2003; 33(6): 448-453.
19. Ogata Y, Matono K, Tsuda H, Ushijima M, Uchida S, Akagi Y, et al. (2015) Randomized Phase II Study of 5-Fluorouracil Hepatic Arterial Infusion with or without Antineoplastons as an Adjuvant Therapy after Hepatectomy for Liver Metastases from Colorectal Cancer. *PLoS ONE* 10(3): e0120064. <https://doi.org/10.1371/journal.pone.0120064>

20. Perrine SP. Fetal globin stimulant therapies in the beta-hemoglobinopathies: Principles and current potential. *Pediatr Ann*, May 2008; 37(5): 339-346.
21. Tsuda H, et al. A novel strategy for remission induction and maintenance in cancer therapy. *Oncology Reports* 2002; 9(1): 65-68.
22. Vickers A. Alternative cancer cures: “Unproven” or “disproven”? *CA: A Cancer Journal for Clinicians*, March 2004; 54(2): 110-118.

POLICY HISTORY:

Adopted for Blue Advantage, June 2006

Available for comment August 1-September 14, 2006

Medical Policy Group, June 2008

Medical Policy Group, June 2010

Medical Policy Group, September 2012 **(3): Effective September 14, 2012 this policy is no longer scheduled for regular literature reviews and updates.**

Medical Policy Group, January 2020

Medical Policy Group, August 2021

Medical Policy Group, September 2022: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.