Antineoplasston Therapy and Sodium Phenylbutyrate

**Number: 0240**

**Policy**

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

I. Aetna considers antineoplasston therapy (auto-urine therapy) and associated medical services experimental and investigational because there is insufficient evidence published in the peer-reviewed medical literature validating the effectiveness of antineoplasston therapy for any indication.

II. Aetna considers services associated with antineoplasston therapy experimental and investigational, including:

- Ancillary diagnostic laboratory, x-rays, MRI or CT scans done to monitor antineoplasston therapy
- Infusion pump and intravenous supplies for use with the infusion pump
- Placement of Hickman catheter.

III. Aetna considers oral antineoplasston therapy or associated physician services for administering and monitoring oral antineoplasston treatment experimental and investigational

**Policy History**

**Last Review** 02/23/2017  
Effective: 04/07/1998  
Next Review: 02/22/2018

**Review History**

**Definitions**

**Additional Information**

**Clinical Policy Bulletin Notes**
because its effectiveness has not been established.

IV. Aetna considers sodium phenylbutyrate medically necessary for the treatment of acute promyelocytic leukemia and malignant glioma.

V. Aetna considers sodium phenylbutyrate experimental and investigational for the treatment of breast cancer, prostate cancer or cancers other than acute promyelocytic leukemia and malignant glioma because its effectiveness for these indications has not been established.

VI. Aetna considers sodium phenylbutyrate experimental and investigational for the treatment of Alzheimer disease, amyotrophic lateral sclerosis, beta-thalassemia, Duchenne muscular dystrophy, inclusion-body myositis, insulin resistance and beta-cell dysfunction, maple syrup urine disease, sickle cell anemia, spinal muscular atrophy, and for all other indications because its effectiveness for these indications has not been established.

Background
Antineoplastons are a group of naturally occurring peptides, which have been hypothesized to have anti-tumor activity. Antineoplaston treatment is offered by the Burzynski Research Institute in Houston, Texas, and has long been a controversial treatment for various types of malignancy.

Antineoplaston therapy is not approved by the Food and Drug Administration (FDA) for any indication, and there are no controlled, peer-reviewed clinical trials to validate the effectiveness of antineoplaston therapy for any indication.

Primitive neuroectodermal tumors (PNETs) are often treated with cranio-spinal radiation and chemotherapy. However, difficulties with conventional therapies can be encountered in very young children, in adult patients at high-risk of complication from standard treatment, as well as in patients with recurrent tumors. In a phase II clinical trial, Burzynski et al
(2005) studied the effect of antineoplaston (ANP) therapy in 13 children, either with recurrent disease or high-risk (median age of 5 years and 7 months, with a range of 1 to 11 years). Medulloblastoma was diagnosed in 8 patients, pineoblastoma in 3 patients, and other PNET in 2 patients. Prior therapies included surgery in 12 patients (1 had biopsy only, suboccipital craniotomy), chemotherapy in 6 patients, and radiation therapy in 6 patients. Six patients had not received chemotherapy or radiation. The treatment consisted of intravenous infusions of 2 formulations of ANP, A10 and AS2-1, and was administered for an average of 20 months. The average dosage of A10 was 10.3 g/kg/day and of AS2-1 was 0.38 g/kg/day. Complete response was accomplished in 23 %, partial response in 8 %, stable disease in 31 %, and progressive disease in 38 % of cases. Six patients (46 %) survived more than 5 years from initiation of ANP; 5 were not treated earlier with radiation therapy or chemotherapy. The serious side effects included single occurrences of fever, anemia, and granulocytopenia. These investigators 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.

Sodium phenylbutyrate (Buphenyl) taken orally is metabolized in the liver into a combination of phenylacetylglutamine and phenylacetate, which then enter the bloodstream. Those 2 chemicals are the prime ingredients of antineoplaston AS2-1.

Sodium phenylbutyrate removes ammonia from the bloodstream, and has been approved by the FDA for use in patients with urea cycle disorders. It also has received an orphan drug designation by the FDA for treatment of acute promyelocytic leukemia. Sodium phenylbutyrate was given an orphan drug designation by the FDA for use as an adjunct to surgery, radiation therapy, and chemotherapy for treatment of patients with primary or recurrent malignant glioma.
Since sodium phenylbutyrate has been approved by the FDA for treatment of other indications, physicians can prescribe it for patients without any danger of legal sanctions or need for compassionate use exemptions. However, there is no adequate evidence in the peer-reviewed published medical literature demonstrating that the use of sodium phenylbutyrate improves the clinical outcomes of patients with cancers of the prostate, breast, or cancers other than acute promyelocytic leukemia and malignant glioma. Current evidence is limited to in-vitro and in-vivo studies and phase I studies. Prospective phase III clinical outcome studies are necessary to determine the clinical effectiveness of sodium phenylbutyrate for cancer.

Brahe et al (2005) stated that spinal muscular atrophy (SMA) is caused by insufficient levels of survival motor neuron (SMN) protein. These researchers found that sodium 4-phenylbutyrate enhances SMN gene expression in-vitro, and that oral administration of sodium 4-phenylbutyrate significantly increases SMN expression in leukocytes of SMA patients. They noted that this finding provides a rationale to further investigate the potential therapeutic effects of sodium 4-phenylbutyrate on patients with SMA.

Wirth et al (2006) stated that the molecular genetic basis of SMA is the loss of function of SMN1. The SMN2 gene, a nearly identical copy of SMN1, has been detected as a promising target for SMA therapy. Both genes encode identical proteins, but differ markedly in their splicing patterns with SMN1 produces full-length (FL)-SMN transcripts only, while the majority of SMN2 transcripts lacks exon 7. Transcriptional SMN2 activation or modulation of its splicing pattern to increase FL-SMN levels is thought to benefit patients with SMA. Drugs such as valproic acid, phenylbutyrate, sodium butyrate, M344 and SAHA can stimulate the SMN2 gene transcription and/or restore the splicing pattern, thereby raising the levels of FL-SMN2 protein. Phase II clinical trials have shown promising results. However, phase III double-blind placebo-controlled studies are needed to prove the effectiveness of these drugs.
Hines and colleagues (2008) stated that increasing hemoglobin F (HbF) appears to be beneficial for patients with sickle cell anemia. These researchers previously reported that daily, oral sodium phenylbutyrate (OSPB) induces HbF synthesis in pediatric as well as adult patients with hemoglobin SS (HbSS). The high doses and need for daily therapy, however, have limited its use. In this study, these investigators reported a patient treated with pulsed-dosing of OSPB for over 3 years. This patient developed a modest, but sustained elevation in HbF over the course of therapy without side effects. Although larger studies are needed, this case demonstrates that pulsed-dosing with OSPB enhances HbF synthesis. Perrine (2008) noted that arginine butyrate, erythropoietin, hydroxyurea, sodium phenylbutyrate, and 5-azacytidine/decitabine have shown efficacy in about 40% to 70% of sickle cell anemia and beta-thalassemia patients. Many responses, although significant, were not completely ameliorating of symptoms or pathology, and trials of new agents with dual actions, or drug combinations, are needed.

In a phase I clinical trial, Lin and associates (2009) determined the minimal effective dose and optimal dose schedule for 5-azacytidine (5-AC) in combination with sodium phenylbutyrate in patients with refractory solid tumors. The pharmacokinetics, pharmacodynamics, and antineoplastic effects were also studied. Three dosing regimens were studied in 27 patients with advanced solid tumors, and toxicity was recorded. The pharmacokinetics of the combination of drugs was evaluated. Repeat tumor biopsies and peripheral blood mononuclear cells (PBMC) were analyzed to evaluate epigenetic changes in response to therapy. Epstein Barr virus titers were evaluated as a surrogate measure for gene re-expression of epigenetic modulation in PBMC. The 3-dose regimens of 5-AC and phenylbutyrate were generally well-tolerated and safe. A total of 48 cycles was administrated to 27 patients. The most common toxicities were bone marrow suppression-related neutropenia and anemia, which were minor. The clinical response rate was disappointing for the combination of agents. One patient showed stable disease for 5 months whereas 26
patients showed progressive disease as the best tumor response. The administration of sodium phenylbutyrate and 5-AC did not seem to alter the pharmacokinetics of either drug. Although there were individual cases of targeted DNA methyltransferase activity and histone H3/4 acetylation changes from paired biopsy or PBMC, no conclusive statement can be made based on these limited correlative studies. The authors concluded that the combination of 5-AC and sodium phenylbutyrate across 3-dose schedules was generally well-tolerated and safe, yet lacked any real evidence for clinical benefit.

In a phase II clinical trial, Cudkowicz and colleagues (2009) examined the safety and pharmacodynamics of escalating dosages of sodium phenylbutyrate (NaPB) in patients with amyotrophic lateral sclerosis (ALS). A total of 40 research subjects at 8 sites enrolled in an open-label study. Study medication was increased from 9 to 21 g/day. The primary outcome measure was tolerability. Secondary outcome measures included adverse events, blood histone acetylation levels, and NaPB blood levels at each dosage. A total of 26 participants completed the 20-week treatment phase. Sodium phenylbutyrate was safe and tolerable. No study deaths or clinically relevant laboratory changes occurred with NaPB treatment. Histone acetylation was decreased by approximately 50 % in blood buffy-coat specimens at screening and was significantly increased after NaPB administration. Blood levels of NaPB and the primary metabolite, phenylacetate, increased with dosage. While the majority of subjects tolerated higher dosages of NaPB, the lowest dose (9 g/day), was therapeutically efficient in improving histone acetylation levels.

Brunetti-Pierri et al (2010) stated that therapy with sodium phenylacetate/benzoate or NaPB in urea cycle disorder patients has been associated with a selective reduction in branched-chain amino acids (BCAA) in spite of adequate dietary protein intake. Based on this clinical observation, these researchers examined the potential of phenylbutyrate
treatment to lower BCAA and their corresponding α-keto acids (BCKA) in patients with classic and variant late-onset forms of maple syrup urine disease (MSUD). They also performed in-vitro and in-vivo experiments to elucidate the mechanism for this effect. These investigators found that BCAA and BCKA are both significantly reduced following phenylbutyrate therapy in control subjects and in patients with late-onset, intermediate MSUD. In-vitro treatment with phenylbutyrate of control fibroblasts and lymphoblasts resulted in an increase in the residual enzyme activity, while treatment of MSUD cells resulted in the variable response that did not simply predict the biochemical response in the patients. In-vivo phenylbutyrate increases the proportion of active hepatic enzyme and unphosphorylated form over the inactive phosphorylated form of the E1α subunit of the branched-chain α-keto acid dehydrogenase complex (BCKDC). Using recombinant enzymes, these researchers showed that phenylbutyrate prevents phosphorylation of E1α by inhibition of the BCKDC kinase to activate BCKDC overall activity, providing a molecular explanation for the effect of phenylbutyrate in a subset of MSUD patients. The authors concluded that phenylbutyrate treatment may be a valuable treatment for reducing the plasma levels of neurotoxic BCAA and their corresponding BCKA in a subset of MSUD patients and studies of its long-term efficacy are indicated.

Xiao et al (2011) noted that chronically elevated free fatty acids contribute to insulin resistance and pancreatic beta (β)-cell failure. Among numerous potential factors, the involvement of endoplasmic reticulum (ER) stress has been postulated to play a mechanistic role. These researchers examined the efficacy of NaPB, a drug with known capacity to reduce ER stress in animal models and in-vitro, on lipid-induced insulin resistance and β-cell dysfunction in humans. A total of 8 over-weight or obese non-diabetic men underwent 4 studies each, in random order, 4 to 6 weeks apart. Two studies were preceded by 2 weeks of oral NaPB (7.5 g/d), followed by a 48-hr i.v. infusion of intralipid/heparin or saline, and 2 studies were preceded by placebo treatment, followed by similar infusions. Insulin
secretion rates (ISR) and sensitivity (SI) were assessed after the 48-hr infusions by hyper-glycemic and hyper-insulinemic-euglycemic clamps, respectively. Lipid infusion reduced SI, which was significantly ameliorated by pre-treatment with NaPB. Absolute ISR was not affected by any treatment; however, NaPB partially ameliorated the lipid-induced reduction in the disposition index (DI = ISR × SI), indicating that NaPB prevented lipid-induced β-cell dysfunction. The authors concluded that these findings suggest that NaPB may provide benefits in humans by ameliorating the insulin resistance and β-cell dysfunction induced by prolonged elevation of free fatty acids. These results need to be validated by well-designed studies.

Corbett et al (2013) noted that neurotrophins, such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), are believed to be genuine molecular mediators of neuronal growth and homeostatic synapse activity. However, levels of these neurotrophic factors decreases in different brain regions of patients with Alzheimer disease (AD). Induction of astrocytic neurotrophin synthesis is a poorly understood phenomenon but represents a plausible therapeutic target because neuronal neurotrophin production is aberrant in AD and other neurodegenerative diseases. These researchers delineated that NaPB, a FDA-approved oral medication for hyperammonemia, induces astrocytic BDNF and NT-3 expression via the protein kinase C (PKC)-cAMP-response element-binding protein (CREB) pathway. Sodium phenylbutyrate treatment increased the direct association between PKC and CREB followed by phosphorylation of CREB (Ser(133)) and induction of DNA binding and transcriptional activation of CREB. Up-regulation of markers for synaptic function and plasticity in cultured hippocampal neurons by NaPB-treated astroglial supernatants and its abrogation by anti-TrkB blocking antibody suggested that NaPB-induced astroglial neurotrophins are functionally active. Moreover, oral administration of NaPB increased the levels of BDNF and NT-3 in the CNS and improved spatial learning and memory in a mouse model of AD. The authors concluded that these findings highlighted a novel neurotrophic
property of NaPB that may be used to augment neurotrophins in the CNS and improve synaptic function in disease states such as AD. These findings from a mouse model of AD need to be examined in well-designed human studies.

Nogalska et al (2014) stated that sporadic inclusion-body myositis (s-IBM) is a severe, progressive muscle disease for which there is no enduring treatment. Pathologically characteristic are vacuolated muscle fibers having: accumulations of multi-protein aggregates, including amyloid-β (Aβ)42 and its toxic oligomers; increased γ-secretase activity; and impaired autophagy. Cultured human muscle fibers with experimentally-impaired autophagy recapitulate some of the s-IBM muscle abnormalities, including vacuolization and decreased activity of lysosomal enzymes, accompanied by increased Aβ42, Aβ42 oligomers, and increased γ-secretase activity. Sodium phenylbutyrate is an orally bioavailable small molecule approved by the FDA for treatment of urea-cycle disorders. These researchers described that NaPB treatment reverses lysosomal dysfunction in an in-vitro model of IBM, involving cultured human muscle fibers. Treatment with NaPB improved lysosomal activity, decreased Aβ42 and its oligomers, decreased γ-secretase activity, and virtually prevented muscle-fiber vacuolization. The authors concluded that NaPB might be considered a potential treatment of s-IBM patients. These in-vitro findings need to be examined in well-designed human studies.

Burrage et al (2014) stated that sodium phenylbutyrate (NaPBA) is a commonly used medication for the treatment of patients with urea cycle disorders (UCDs). Previous reports involving small numbers of patients with UCDs have shown that NaPBA treatment can result in lower plasma levels of the branched-chain amino acids (BCAA) but this has not been studied systematically. From a large cohort of patients (n = 553) with UCDs enrolled in the Longitudinal Study of Urea Cycle Disorders, a collaborative multi-center study of the Urea Cycle Disorders Consortium, these researchers examined if treatment with NaPBA leads to a decrease in plasma BCAA levels. Their
analysis showed that NaPBA use independently affected the plasma BCAA levels even after accounting for multiple confounding co-variates. Moreover, NaPBA use increased the risk for BCAA deficiency. This effect of NaPBA appeared specific to plasma BCAA levels, as levels of other essential amino acids are not altered by its use. This study, in an unselected population of UCD subjects, is the largest to analyze the effects of NaPBA on BCAA metabolism and potentially has significant clinical implications. These findings indicated that plasma BCAA levels should to be monitored in patients treated with NaPBA since patients taking the medication are at increased risk for BCAA deficiency. On a broader scale, these findings could open avenues to explore NaPBA as a therapy in maple syrup urine disease and other common complex disorders with dysregulation of BCAA metabolism.

An UpToDate review on “Overview of maple syrup urine disease” (Bodamer, 2014) and other reviews of MSUD (Strauss, et al., 2013; McKusick, et al., 2013) do not mention sodium phenylbutyrate as a therapeutic option.

In an open label, non-blinded, randomized, phase II clinical trial, Ogata and colleagues (2015) compared the effectiveness of hepatic arterial infusion (HAI) with 5-fluorouracil, with or without antineoplastons as a post-operative therapy for colorectal metastasis to the liver. A total of 65 patients with histologically confirmed metastatic colon adenocarcinoma in liver, who had undergone hepectomy, and/or thermal ablation for liver metastases were enrolled between 1998 to 2004. Patients were randomly assigned to receive systemic antineoplastons (A10-I infusion followed by per-oral AS2-1) plus HAI (AN arm) or HAI alone (control arm) based on the number of metastases and presence/absence of extra-hepatic metastasis at the time of surgery. Primary end-point was cancer-specific survival (CSS); secondary end-points were relapse-free survival (RFS), status and extent of recurrence, salvage surgery (rate) and toxicity. Overall survival was not statistically improved (p = 0.105) in the AN arm (n = 32). Relapse-free survival was not significant (p = 0.343).
Nevertheless, the CSS rate was significantly higher in the AN arm versus the control arm (n = 33) with a median survival time of 67 months (95 % confidence interval [CI]: 43 to not calculated) versus 39 months (95 % CI: 28 to 47) (p = 0.037) and 5 year CSS rate of 60 % versus 32 % respectively. Cancer recurred more often in a single organ than in multiple organs in the AN arm versus the control arm. The limited extent of recurrent tumors in the AN arm meant more patients remained eligible for salvage surgery. Major adverse effects of antineoplastons were fullness of the stomach and phlebitis. No serious toxicity, including bone marrow suppression, liver or renal dysfunction, were found in the AN arm. The authors concluded that antineoplastons (A10 Injection and AS2-1) might be useful as adjunctive therapy in addition to HAI after hepatectomy in colorectal metastases to the liver.

**Duchenne Muscular Dystrophy:**

Begam and colleagues (2016) performed a placebo-controlled pre-clinical study to determine if sodium 4-phenylbutyrate (4PB) can reduce contraction-induced myofiber damage in the mdx mouse model of Duchenne muscular dystrophy (DMD). At 72 hours post-eccentric contractions, 4PB significantly increased contractile torque and reduced myofiber damage and macrophage infiltration. The authors concluded that 4PB might modify disease severity in patients with DMD.
<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C00.0 - D49.9</td>
<td>Neoplasms</td>
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<tr>
<td>G12.21</td>
<td>Amyotrophic lateral sclerosis</td>
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<tr>
<td>Z51.0</td>
<td>Encounter for antineoplastic radiation therapy</td>
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<tr>
<td>Z51.11 - Z51.12</td>
<td>Encounter for antineoplastic chemotherapy and immunotherapy</td>
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**Sodium phenylbutyrate:**

No specific code.

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C71.0 - C72.9</td>
<td>Malignant neoplasm of brain and other and unspecified parts of nervous system [malignant glioma]</td>
</tr>
<tr>
<td>C92.40 - C92.42</td>
<td>Acute promyelocytic leukemia</td>
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**ICD-10 codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C00.0 - C70.9</td>
<td>Malignant neoplasm [other than promyelocytic leukemia and malignant glioma]</td>
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<tr>
<td>C73 - C92.32</td>
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<tr>
<td>C92.50 - C96.9</td>
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<tr>
<td>D56.0 - D56.9</td>
<td>Thalassemias</td>
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<td>D57.00 - D57.819</td>
<td>Sickle-cell disease</td>
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<tr>
<td>E71.0</td>
<td>Maple syrup urine disease</td>
</tr>
<tr>
<td>E88.81</td>
<td>Metabolic syndrome [insulin resistance]</td>
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<tr>
<td>G12.0 - G12.9</td>
<td>Spinal muscular atrophy</td>
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<tr>
<td>G30.0 - G30.9</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>G72.41</td>
<td>Inclusion body myositis [IBM]</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


33. Dyer ES, Paulsen MT, Markwart SM, et al. Phenylbutyrate inhibits the invasive properties of prostate and breast


73. Burzynski SR, Janicki TJ, Weaver RA, Burzynski B. Targeted


82. Xiao C, Giacca A, Lewis GF. Sodium phenylbutyrate, a drug with known capacity to reduce endoplasmic reticulum stress, partially alleviates lipid-induced insulin resistance and {beta}-cell dysfunction in humans. Diabetes. 2011;60(3):918-924.


87. Bodamer OA. Overview of maple syrup urine disease. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2014.


Amendment to
Aetna Clinical Policy Bulletin Number: 0240 – Antineoplaston Therapy and Sodium Phenylbutyrate

There are no amendments for Medicaid.