Prior Authorization Review Panel  
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

<table>
<thead>
<tr>
<th>Plan: Aetna Better Health</th>
<th>Submission Date: 02/01/2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy Number: 0240</td>
<td>Effective Date:</td>
</tr>
<tr>
<td></td>
<td>Revision Date: 12/27/2019</td>
</tr>
<tr>
<td>Policy Name: Antineoplaston Therapy and Sodium Phenylbutyrate</td>
<td></td>
</tr>
</tbody>
</table>

**Type of Submission** – Check all that apply:

- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

**CPB 0240 Antineoplaston Therapy and Sodium Phenylbutyrate**

This CPB is revised to remove acute promyelocytic leukemia and malignant glioma as medically necessary indications for sodium phenylbutyrate. This CPB is revised to provide continuation criteria for sodium phenylbutyrate.

<table>
<thead>
<tr>
<th>Name of Authorized Individual (Please type or print):</th>
<th>Signature of Authorized Individual:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Bernard Lewin, M.D.</td>
<td>Bernard Lewin, M.D.</td>
</tr>
</tbody>
</table>

Revised July 22, 2019
Antineoplaston Therapy and Sodium Phenylbutyrate

Number: 0240

Policy

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

I. Aetna considers antineoplaston 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 antineoplaston therapy for any indication.

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

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

III. Aetna considers oral antineoplaston therapy or associated physician services for administering and monitoring oral antineoplaston treatment experimental and investigational because its effectiveness has not been established.

Policy History

Last Review
12/27/2019
Effective: 04/07/1998
Next Review: 02/27/2020

Review History

Definitions

Additional Information

Clinical Policy Bulletin
Notes
IV. Aetna considers sodium phenylbutyrate medically necessary for the treatment of urea cycle disorders when the diagnosis is confirmed by enzymatic, biochemical, or genetic testing. Continued treatment with sodium phenylbutyrate is considered medically necessary for persons who demonstrate disease stability or improvement.

V. Aetna considers continued treatment with sodium phenylbutyrate medically necessary for members who are experiencing benefit from therapy as evidenced by a reduction in plasma ammonia levels from baseline.

VI. Aetna considers sodium phenylbutyrate experimental and investigational for the treatment of breast cancer, non-small-cell lung cancer, oral squamous cell carcinoma, prostate cancer or other cancers because its effectiveness for these indications has not been established.

VII. Aetna considers sodium phenylbutyrate experimental and investigational for the treatment of Alzheimer disease, amyotrophic lateral sclerosis, beta-thalassemia, Duchenne muscular dystrophy, hepatic encephalopathy associated with cirrhosis, inclusion-body myositis, insulin resistance and beta-cell dysfunction, ischemic stroke, 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.

**Dosing Recommendations**

The usual total daily dose of Buphenyl Tablets and Powder for patients with urea cycle disorders is 450–600 mg/kg/day in patients weighing less than 20 kg, or 9.9–13.0 g/m²/day in larger patients. The safety or efficacy of doses in excess of 20 grams (40 tablets) per day has not been established.

Source: Buphenyl prescribing information.
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 hepatectomy, 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 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 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.
Hepatic Encephalopathy associated with Cirrhosis

Rahimi and Rockey (2016) noted that hepatic encephalopathy (HE) is a major complication in patients with decompensated cirrhosis, leading to higher re-admission rates causing a profound burden of disease and considerable health care costs. Because ammonia is thought to play a crucial role in the pathogenesis of HE, therapies directed at reducing ammonia levels are now being aggressively developed. Ammonia scavengers such as AST-120 (spherical carbon adsorbent), glycerol phenylbutyrate (GPB), sodium phenylacetate or sodium benzoate, and ornithine phenylacetate have been used to improve HE symptoms. A new approach, bowel cleansing with polyethylene glycol 3350, appeared to be a promising therapy, with a recent study demonstrating a more rapid improvement in overt HE (at 24 hours after treatment) than lactulose.

Extracorporeal devices, although now used primarily in research settings, have also been utilized in patients with refractory HE, but are not approved for clinical management. The authors stated that available evidence suggested that GPB decreased the likelihood of hospitalization for cirrhotic patients with recurrent HE when compared with placebo, by lowering ammonia levels. Overall, GPB was considered to be safe among cirrhotic patients with recurrent HE; however, larger randomized controlled trials (RCTs) are needed to further establish the role of GPB in patients with HE.

Weiss and colleagues (2018) stated that HE influences short-term and long-term prognoses. Recently, GPB has shown to be effective in preventing the occurrence of HE in a RCT. In a preliminary study, these researchers examined the benefits of SPB in cirrhotic patients admitted to intensive care unit (ICU) for overt HE, in terms of ammonia levels decrease, neurological improvement, and survival. Cirrhotic patients who presented with overt HE, ammonia levels greater than 100 μmol/L, and did not display any contra-indication were included; SPB was administered at 200 mg/kg/day. Control group included historical controls treated by standard therapy, matched for age, sex, MELD score, and severity of HE. A total of 18 patients were included and treated with SPB (age of 59 years [45 to 68], male gender: 15 [83 %], Child-Pugh B: 8 [44 %], Child-Pugh C: 10 [56 %], and MELD score of 16 [13 to 23]). Ammonia levels significantly decreased in the SPB as compared to the control group from inclusion to 12 hours and from inclusion to 48 hours (p
The proportion of patients displaying neurological improvement was only higher in the SPB-treated group as compared to controls at ICU discharge (15 [83 %] versus 9 [50 %], p = 0.0339). ICU discharge survival was significantly higher in patients treated with SPB (17 [94 %] versus 9 [50 %], p = 0.0017). The authors concluded that in cirrhotic patients with overt HE, SPB could be effective in reducing ammonia levels and might be effective in improving neurological status and ICU discharge survival. However, they stated that more extensive data, especially a RCT, are needed.

Ischemic Stroke

Yang and associates (2017) noted that oxidative stress and mitochondrial dysfunction play critical roles in ischemia/reperfusion (I/R) injury; DJ-1 is an endogenous anti-oxidant that attenuates oxidative stress and maintains mitochondrial function, likely acting as a protector of I/R injury. These researchers examined the protective effect of a possible DJ-1 agonist, SPB, against I/R injury by protecting mitochondrial dysfunction via the up-regulation of DJ-1 protein. Pre-treatment with SPB up-regulated the DJ-1 protein level and rescued the I/R injury-induced DJ-1 decrease about 50 % both in vivo and in-vitro; SPB also improved cellular viability and mitochondrial function and alleviated neuronal apoptosis both in cell and animal models; these effects of SPB were abolished by DJ-1 knockdown with siRNA. Furthermore, SPB improved the survival rate approximately 20 % and neurological functions, as well as reduced about 50 % of the infarct volume and brain edema, of middle cerebral artery occlusion mice 23 hours after re-perfusion. The authors concluded that these findings demonstrated that pre-conditioning of SPB possessed a neuroprotective effect against cerebral I/R injury by protecting mitochondrial function dependent on the DJ-1 up-regulation, suggesting that DJ-1 is a potential therapeutic target for clinical ischemic stroke.

Urea Cycle Disorders

Haberle and colleagues (2012) stated that urea cycle disorders (UCDs) are inborn errors of ammonia detoxification/arginine synthesis due to defects affecting the catalysts of the Krebs-Henseleit cycle (5 core enzymes, 1 activating enzyme and 1 mitochondrial ornithine/citrulline antiporter) with an estimated incidence of 1:8,000. Patients present with
hyper-ammonemia either shortly after birth (approximately 50%) or, later at any age, leading to death or to severe neurological handicap in many survivors. Despite the existence of effective therapy with alternative pathway therapy and liver transplantation, outcomes remain poor. This may be related to under-recognition and delayed diagnosis due to the non-specific clinical presentation and insufficient awareness of health care professionals because of disease rarity. These guidelines aimed at providing a trans-European consensus to: guide practitioners, set standards of care and help awareness campaigns. To achieve these goals, the guidelines were developed using a Delphi methodology, by having professionals on UCDs across 7 European countries to gather all the existing evidence, scored it according to the SIGN evidence level system and drew a series of statements supported by an associated level of evidence. The guidelines were revised by external specialist consultants, unrelated authorities in the field of UCDs and practicing pediatricians in training. Although the evidence degree did hardly ever exceed level C (evidence from non-analytical studies like case reports and series), it was sufficient to guide practice on both acute and chronic presentations, addressed diagnosis, management, monitoring, outcomes, and psychosocial and ethical issues. Also, it identified knowledge voids that must be filled by future research. The authors believed these guidelines will help to harmonize practice, set common standards and spread good practices with a positive impact on the outcomes of UCD patients. These investigators stated that ammonia scavengers sodium benzoate, sodium phenylacetate or PBA are the mainstay drugs for bypassing the urea cycle, by conjugation of benzoate with glycine to generate hippurate, or of phenylacetate (phenylbutyrate is a precursor of phenylacetate) with glutamine to generate phenylacetylglutamine. These conjugates are excreted in the urine.

According to the prescribing information, buphenyl (sodium phenylbutyrate) is indicated as adjunctive therapy in the chronic management of patients with UCDs involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase. It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the 1st month of life) who have a history of hyper-ammonemic encephalopathy.
It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyper-ammonemia should be treated as a life-threatening emergency.

Sodium Phenylbutyrate for the Treatment of Non-Small-Cell Lung Cancer

Al-Keilani and colleagues (2018) stated that chemotherapy resistance is the main cause of the marginal clinical benefit of platinum-based chemotherapy and tyrosine kinase inhibitors in advanced non-small-cell lung cancer (NSCLC). Thus, the identification of new therapeutic agents that can enhance the sensitivity of these drugs is of clinical importance. Histone deacetylase inhibitors (HDACIs) are emerging as new promising agents with strong anti-proliferative effects against different types of cancers. These investigators examined the synergistic potential of SPB added on top of standard chemotherapy used against NSCLC. They evaluated the ability of SPB to overcome the resistance of NSCLC cell lines to cisplatin, gefitinib, and erlotinib. MTT cell proliferation assay was used to measure the anti-cancer effects of cisplatin, erlotinib, or gefitinib alone or combined with various concentrations of SPB against A549, Calu1, and H1650 NSCLC cell lines. Synergism was estimated by measuring synergy value (R), which is equal to the ratio of IC50 (the concentration of an inhibitor where the response (or binding) is reduced by half) of each primary drug alone divided by combination IC50s.

Student's t-test analysis was used to evaluate the potential differences between IC50 values. ANOVA followed by Tukey's post-hoc was used to evaluate the potential differences among monotherapy and combination treatment groups. Analyses were performed using R 3.3.2 software; p-value < 0.05 was considered to be statistically significant. Sodium phenylbutyrate was shown to inhibit the growth of A549, Calu1, and H1650 cell lines in a dose-dependent manner (IC50 10, 8.53, and 4.53 mM, respectively). Furthermore, the addition of SPB along with cisplatin, erlotinib, or gefitinib to A549, Calu1, and H1650 cell lines resulted in a synergistic anti-proliferative effect against the 3 NSCLC cell lines (R > 1.6, p-value < 0.05), thus suggesting that SPB could potentiate the effect of cisplatin, erlotinib, and gefitinib on A549, Calu1, and H1650 cell lines. The authors concluded that current findings suggested a potential role of SPB as a sensitizing agent in NSCLC.
Sodium Phenylbutyrate for the Treatment of Oral Squamous Cell Carcinoma

Qian and colleagues (2018) noted that SPB as a salt of 4-phenylbutyric acid (4-PBA) has been reported to be an ammonia scavenger, histone deacetylase inhibitor, and an endoplasmic reticulum stress inhibitor in various diseases, including neurological diseases, inflammatory disorders, and carcinogenesis. Although phenylbutyrate showed effective anti-tumor properties in many cancers, its role in oral squamous cell carcinoma (OSCC) remains further characterized. In this study, the OSCC cell lines CAL27, HSC3, and SCC4 were treated with a series of doses of SPB for different times. The IC50 of 3 cell lines for SPB was determined to be 4.0, 3.7, and 3.0 mM. The CCK-8 assay indicated that the treatment of SPB induced continuous inhibition of cell vitality of 3 cell lines. Apoptosis was assessed by Hoechst assay that showed that SPB could significantly promote cell apoptosis. Moreover, the apoptosis-related pathway was analyzed, and the results showed that the expression of anti-apoptosis factor BCL-2 was down-regulated by SPB but the cleavage of caspase-3 was increased. Meanwhile, it was found that SPB also impaired the migration and invasion of OSCC cells in-vitro. Mechanistically, the transforming growth factor-β (TGFβ) related epithelial-mesenchymal transition (EMT) was inhibited by SPB with decreased mesenchymal marker N-cadherin and increased epithelial marker E-cadherin. Furthermore, the anti-tumor effect of SPB in-vivo was also demonstrated. The administration of SPB induced remarkably tumor regression with decreased tumor volume, and the TGFβ level and EMT phenotype in-vivo were also inhibited. These data demonstrated that the treatment of SPB could function as anti-tumor therapeutics for OSCC.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antineoplaston therapy:</td>
<td></td>
</tr>
<tr>
<td>No specific code.</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>C00.0 - D49.9</td>
<td>Neoplasms</td>
</tr>
<tr>
<td>G12.21</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>Z51.0</td>
<td>Encounter for antineoplastic radiation therapy</td>
</tr>
<tr>
<td>Z51.11 - Z51.12</td>
<td>Encounter for antineoplastic chemotherapy and immunotherapy</td>
</tr>
</tbody>
</table>

**Sodium phenylbutyrate:**

No specific code.

ICD-10 codes covered if selection criteria are met:

- **E72.20 - E72.29** Disorders of urea cycle metabolism
- **E72.4** Disorders of ornithine metabolism

ICD-10 codes not covered for indications listed in the CPB:

- **C00.0 - C70.9** Malignant neoplasm [other than promyelocytic leukemia and malignant glioma]
- **C73 - C92.32 C92.50 - C96.9**
- **D56.0 - D56.9** Thalassemias
- **D57.00 - D57.819** Sickle-cell disease
- **E71.0** Maple syrup urine disease
- **E88.81** Metabolic syndrome [insulin resistance]
- **G12.0 - G12.9** Spinal muscular atrophy
### Code | Code Description
--- | ---
G30.0 - G30.9 | Alzheimer's disease
G71.01 | Duchenne or Becker muscular dystrophy
G72.41 | Inclusion body myositis [IBM]
I63.00 - I63.9 | Cerebral infarction [ischemic stroke]
K72.01, K72.11, K72.91 | Hepatic encephalopathy

The above policy is based on the following references:


42. Wargovich MJ, Jimenez A, McKee K, et al. Efficacy of potential chemopreventive agents on rat colon aberrant crypt formation and


65. Burzynski SR, Lewy RI, Weaver RA, et al. Phase II study of antineoplaston A10 and AS2-1 in patients with recurrent diffuse...


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.

88. Strauss KA, Puffenberger EG, Morton DH. Maple syrup urine disease. In: GeneReviews [Internet]. Pagon RA, Adam MP, Ardinger


For the Pennsylvania Medical Assistance plan sodium phenylbutyrate is also considered medically necessary for the treatment of urea cycle disorders.

For the Pennsylvania Medical Assistance Plan, effective 1/1/20 medication coverage requests for medications on the statewide preferred drug list will be reviewed using the guidelines for determination of medical necessity developed by the Pennsylvania Department of Human Services.