AETNA BETTER HEALTH®

Clinical Policy Bulletin:
Alzheimer's Disease: Experimental Treatments

Revised April 2014

Number: 0788

Policy

Aetna considers the following treatments for Alzheimer's disease (AD) experimental and investigational because their effectiveness for this indication has not been established (not an all inclusive list).

Adoptive immunotherapy (see CPB 0641 - Adoptive Immunotherapy and and Cellular Therapy)
Applied behavior analysis
Bapineuzumab
Beta-amyloid degrading enzymes including cathepsin B, neprilysin, and neprilysin-2
Celecoxib (Celebrex)
Continuous drainage of cerebral spinal fluid
Deep brain stimulation (see CPB 0208 - Deep Brain Stimulation)
Etanercept (Enbrel) (see CPB 0315 - Enbrel (Etanercepti))
Growth hormone secretagogues (see CPB 0170 - Growth Hormone (GH) and Growth Hormone Antagonists)
Hormone replacement therapy/estrogen replacement therapy (for women with AD)
Huperzine A
Hyperbaric oxygen therapy (HBOT) (see CPB 0172 - Hyperbaric Oxygen Therapy (HBOT))
Indomethacin
Insulin (nasal spray)
Intravenous immunoglobulins (IVIG) (see CPB 0206 - Parenteral Immunoglobulins)
Leuprolide (CPB 0501 - Gonadotropin-Releasing Hormone Analogs and Antagonists)
Light therapy
Metal protein attenuating compounds (e.g., clioquinol)
Methylthioninium chloride
Mifepristone (RU 486) (see CPB 0465 - Mifepristone (RU486))
Naproxen
PBT2 (a metal-protein attenuating compound)
Plasma exchange and hemapheresis
Semagacestat
Solanezumab
Statins
Stem cell therapy (including bone marrow derived mesenchymal stem cells)
Tarenflurbil
Transcranial magnetic stimulation/direct current stimulation (see CPB 0469 - Transcranial Magnetic Stimulation and Cranial Electrical Stimulation)
Vaccine therapy (e.g., active and passive amyloid vaccines)
Vagus nerve stimulation (see CPB 0191 - Vagus Nerve Stimulation).

Background

Alzheimer's disease (AD) is the most common cause of dementia characterized by progressive neuro-degeneration. The treatment of patients with AD has been an intensive research topic in the past several decades. Current treatments mainly target towards cholinergic deficiency. Cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) remain the preferred therapy for early and intermediate AD, while memantine (a glutamate antagonist) is also approved for advanced AD. Advances in knowledge of the pathogenesis of the disease as well as an increase in disease burden have resulted in research on innovative therapies. Epidemiological studies have suggested that non-steroidal anti-inflammatory drugs, estrogen, HMG-CoA reductase inhibitors (statins) or tocopherol (vitamin E) can prevent AD. However, prospective, randomized studies have not convincingly been able to demonstrate clinical effectiveness. Other experimental approaches include adoptive immunotherapy, continuous drainage of cerebral spinal fluid (CSF), deep brain stimulation, hormone replacement therapy, hyperzine A, hyperbaric oxygen therapy, intra-nasal insulin, intravenous immunoglobulins (IVIG), leuprolide, metal protein attenuating compounds (e.g., clioquinol), mifepristone (RU 486), stem cell therapy, transcranial magnetic stimulation/direct current stimulation, vaccine therapy, and vagus nerve stimulation (VNS). However, data on these experimental therapies remain equivocal at best.
In a review on AD, Ballard et al (2011) listed several proposed disease-modifying treatments for AD -- methylthioninium chloride (a tau aggregation inhibitor), PBT2 (a copper or zinc modulator), and semagacestat (a secretase inhibitor). The clinical value of these agents in the treatment of patients with AD needs to be validated by well-designed studies.

Semagacestat is a small-molecule γ-secretase inhibitor that was developed as a potential treatment for AD. Doody et al (2013) conducted a double-blind, placebo-controlled trial in which 1,537 patients with probable AD underwent randomization to receive 100 mg of semagacestat, 140 mg of semagacestat, or placebo daily. Changes in cognition from baseline to week 76 were assessed with the use of the cognitive subscale of the ADAS-Cog, on which scores range from 0 to 70 and higher scores indicate greater cognitive impairment, and changes in functioning were assessed with the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL) scale, on which scores range from 0 to 78 and higher scores indicate better functioning. A mixed-model repeated-measures analysis was used. The trial was terminated before completion on the basis of a recommendation by the data and safety monitoring board. At termination, there were 189 patients in the group receiving placebo, 153 patients in the group receiving 100 mg of semagacestat, and 121 patients in the group receiving 140 mg of semagacestat. The ADAS-Cog scores worsened in all 3 groups (mean change of 6.4 points in the placebo group, 7.5 points in the group receiving 100 mg of the study drug, and 7.8 points in the group receiving 140 mg; p = 0.15 and p = 0.07, respectively, for the comparison with placebo). The ADCS-ADL scores also worsened in all groups (mean change at week 76, -9.0 points in the placebo group, -10.5 points in the 100-mg group, and -12.6 points in the 140-mg group; p = 0.14 and p < 0.001, respectively, for the comparison with placebo). Patients treated with semagacestat lost more weight and had more skin cancers and infections, treatment discontinuations due to adverse events, and serious adverse events (p < 0.001 for all comparisons with placebo). Laboratory abnormalities included reduced levels of lymphocytes, T cells, immunoglobulins, albumin, total protein, and uric acid and elevated levels of eosinophils, monocytes, and cholesterol; the urine pH was also elevated. The authors concluded that as compared with placebo, semagacestat did not improve cognitive status, and patients receiving the higher dose had significant worsening of functional ability. Semagacestat was associated with more adverse events, including skin cancers and infections.

**Vagus Nerve Stimulation:**

In a open-label, pilot study (n = 10), Sjögren and colleagues (2002) examined the effect of VNS on cognition in patients with AD. Before implantation of the vagus stimulator, patients underwent neuropsychological tests such as Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and Mini-Mental State Examination (MMSE), computerized tomography of the brain, medical/neurological and psychological examinations (status evaluation), and lumbar puncture with investigation of the CSF. The presence of depression was rated using the Montgomery-Asberg Depression Rating Scale. Vagus nerve stimulation commenced 2 weeks after the implantation, and patients were followed -up with regular investigations and tests over 6 months. Response was defined as improvement or absence of impairment in ADAS-Cog and MMSE scores after 3
and 6 months. After 3 months of treatment, 7 of 10 patients were responders according to the ADAS-Cog (median improvement of 3.0 points), and 9 of 10 patients were responders according to the MMSE (median improvement of 1.5 points). After 6 months of treatment, 7 patients were responders on the ADAS-Cog (median improvement of 2.5 points), and 7 patients were responders on the MMSE (median improvement of 2.5 points). Vagus nerve stimulation was well-tolerated, and its side effects were mild and transient. The authors concluded that the findings of this pilot study suggested a positive effect of VNS on cognition in patients with AD. They stated that further studies are needed.

In a follow-up report of the afore-mentioned study, Merrill and co-workers (2006) presented data through 1 year of VNS. Responder rates for ADAS-Cog and MMSE were measured as improvement or absence of decline from baseline. Global change, depression, as well as quality of life (QOL) were also assessed. Cerebrospinal fluid levels for total tau, tau phosphorylated at Thr181 (phosphotau), and beta amyloid 42 (Abeta 42) were measured by standardized enzyme-linked immunosorbent assay. After 1 year, 7 (41.2 %) of 17 patients and 12 (70.6 %) of 17 patients improved or did not decline from baseline on the ADAS-Cog and MMSE, respectively. Twelve of 17 patients were rated as having no change or some improvement from baseline on the Clinician Interview-Based Impression of Change (CIBIC). No significant decline in mood, behavior, or QOL occurred during 1 year of treatment. The median change in CSF tau at 1 year was a reduction of 4.8 % (p = 0.057), with a 5.0 % increase in phosphotau (p= 0.040; n = 14). The authors concluded that the findings of this study supported long-term tolerability of VNS among patients with AD and warranted further investigation. In this regard, Ansari et al (2007) noted that clinical trials are ongoing to examine VNS as a potential treatment for cognitive deficits in AD.

**Intravenous Immunoglobulins:**

Active or passive immunization has been reported to mitigate plaque pathology in murine models of AD. It has been shown that antibodies against Abeta are present in human IVIG preparations, which specifically recognize and inhibit the neurotoxic effects of Abeta. In a pilot study, Dodel and colleagues (2004) reported the findings of treatment with IVIG in patients with AD. A total of 5 patients with AD were enrolled and received monthly IVIG over a 6-month period. Effectiveness assessment included total Abeta/Abeta (1-42) measured in the CSF/serum as well as effects on cognition (ADAS-Cog; Consortium to Establish a Registry for Alzheimer’s Disease [CERAD]) at baseline and at 6 months following IVIG. Following IVIG treatment, total Abeta levels in the CSF decreased by 30.1 % (17.3 % to 43.5 %) compared to baseline (p < 0.05). Total Abeta increased in the serum by 233 % (p < 0.05). No significant change was found in Abeta (1-42) levels in the CSF/serum. Using ADAS-Cog, an improvement of 3.7 +/- 2.9 points was detected. Scores in MMSE were essentially unchanged (improved in 4 patients, stable in 1 patient) following IVIG treatment compared to baseline. The authors concluded that although the sample size of this pilot study was too small to draw a clear conclusion, the results provided evidence for a more detailed investigation of IVIG for the treatment of AD. Furthermore, Solomon (2007) noted that preliminary
results indicated that IVIG warrants further study into its potential to deliver a controlled immune attack on Abeta, avoiding the immune toxicities that have had a negative impact on the first clinical trials of vaccine against the peptide.

**Mifepristone:**

DeBattista and Belanoff (2005) noted that AD is often associated with abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis. Elevated cortisol levels in AD may in turn be associated with a more rapid progression of the illness. Furthermore, elevated cortisol levels may directly contribute to cognitive deficits in patients with AD. Mifepristone (RU 486) is a potent antagonist of the glucocorticoid receptor and blocks the central actions of cortisol. These researchers noted that given the limited options for the treatment of AD, mifepristone represents an innovative and promising therapeutic approach for this disease. However, there is currently a lack of well-designed studies to support this approach in treating AD.

In a pilot study, Pomara et al (2006) examined the cortisol response to RU 486 in patients with AD. A total of 9 AD subjects were randomized in a placebo-controlled parallel study: 4 in the placebo group and 5 in the RU 486 group. Subjects received oral doses of RU 486 (200 mg) or placebo daily for 6 weeks. Morning plasma cortisol was determined at baseline, at 12 hours following the first study drug dose, and weekly thereafter. Mifepristone resulted in a significant increase in cortisol levels \( F(1,6) = 65.32; p < 0.001 \). The magnitude of this increase grew over the course of the study \( F(1,6) = 63.17; p < 0.001 \), was not related to cortisol suppression after dexamethasone and appeared greater than that reported in the literature in younger populations in response to the same drug regimen. The authors concluded that further studies with age-matched controls should be done to determine possible AD-related changes in this response.

Dhikav and Anand (2007) stated that mifepristone has intrinsic neuroprotective and antioxidant potential which could provide benefits to patients with mild AD or with milder cognitive impairment. Moreover, appropriate dose, duration, safety and effectiveness need to be worked out.

**Leuprolide:**

Estrogen and other sex hormones have received much attention for their speculative role in AD, however a direct connection between estrogen and the pathogenesis of AD remains elusive and somewhat contradictory. While there is a large body of evidence suggesting that estrogen is neuro-protective, and that hormone replacement therapy (HRT) at the onset of menopause reduces the risk of developing AD decades later, studies such as the Women's Health Initiative showed that HRT initiated in elderly women increases the risk of dementia. Although estrogen continues to be examined, the disparity of findings involving HRT has resulted in investigation of other hormones of the HPA axis such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Casadesus and associates (2006) proposed that LH, rather than estrogen, is the critical player in the pathogenesis of AD since both men and women experience a 3- to 4-fold increase in LH with aging, and LH receptors are found throughout the brain following a regional pattern similar to that exhibited by neurons affected in AD. With respect to disease, serum LH level is increased in women with AD relative to
non-diseased controls, and levels of LH in the brain are also elevated in AD. The authors proposed that elevated levels of LH may be an instigator responsible for the aberrant re-activation of the cell cycle that is observed in AD. Wilson et al (2007) stated that leuprolide acetate, a synthetic nonapeptide that suppresses gonadotrope secretion of LH and FSH, which subsequently suppresses gonadal sex steroid production, is presently being tested for the treatment of AD.

**Hormone Replacement Therapy:**

In a Cochrane review on HRT to maintain cognitive function in women with dementia, Hogervorst and colleagues (2009) examined the effects of HRT (estrogens combined with a progestagen) or estrogen replacement therapy (ERT; estrogens only) compared with placebo in randomized controlled trials (RCTs) on cognitive function of post-menopausal women with dementia. All double-blind RCTs into the effect of ERT or HRT for cognitive function with a treatment period of at least 2 weeks in post-menopausal women with AD or other types of dementia were selected. Abstracts of the references retrieved by the searches were read by two reviewers independently in order to discard those that were clearly not eligible for inclusion. The two reviewers studied the full text of the remaining references and independently selected studies for inclusion. Any disparity in the ensuing lists was resolved by discussion with all reviewers in order to arrive at the final list of included studies. The selection criteria ensured that the blinding and randomization of the included studies was adequate. The 2 reviewers also assessed the quality of other aspects of the included trials. A total of 7 trials including 351 women with AD were analyzed. Because different drugs were used at different studies it was not possible to combine more than 2 studies in any analysis. On a clinical global rating, clinicians scored patients taking conjugated equine estrogens (CEE) as significantly worse compared with the placebo group on the Clinical Dementia Rating scale after 12 months (overall WMD = 0.35, 95 % confidence interval [CI]: 0.01 to 0.69, z = 1.99, p < 0.05). Patients taking CEE had a worse performance on the delayed recall of the Paragraph Test (overall WMD = -0.45, 95 % CI: -0.79 to -0.11, z = 2.60, p < 0.01) after 1 month than those taking placebo. They had a worse performance on Finger Tapping after 12 months (WMD = -3.90, 95 % CI: -7.85 to 0.05, z = 1.93, p < 0.05). Limited positive effects were found for the lower dosage of CEE (0.625 mg/day) which showed a significant improvement in MMSE score only when assessed at 2 months, and disappeared after correction for multiple testing. No significant effects for MMSE were found at longer end points (3, 6 and 12 months of treatment). With a dosage of 1.25 mg/d CEE, short-term significant effects were found for Trial-Making test B at 1 month and Digit Span backward at 4 months. After 2 months of transdermal diestradiol (E2) treatment, a highly significant effect was observed for the word recall test (WMD = 6.50, 95 % CI: 4.04 to 8.96, z = 5.19, p < 0.0001). No other significant effects were found for other outcomes measured. The authors concluded that currently, HRT or ERT for cognitive improvement or maintenance is not indicated for women with AD.

**Statins:**

Zhou and associates (2007) performed a meta-analysis to evaluate the preventive and treatment effects of statins on dementia and AD onset. Relevant studies were systematically identified, and data were abstracted according to pre-defined criteria. These investigators used a fixed-effects model and a random-effects
model to compute pooled relative risks and to assess statistical heterogeneity. 
The pooled crude odds ratios in statin users as compared with non-users were 
0.67 (95% CI: 0.54 to 0.82) in the dementia group and 0.81 (95% CI: 0.64 to 
1.02) in the AD group. The pooled adjusted relative risks calculated by random-
effects model were 0.77 (95% CI: 0.45 to 1.30) in the dementia group and 0.81 
(95% CI: 0.56 to 1.16) in the AD group. The authors concluded that the use of 
statins did not show a beneficial effect on the risk of dementia or AD. They noted 
that further study and independent confirmation of the association between the 
use of statin and dementia/AD in larger clinical trials are warranted.

Bifulco et al (2008) noted that statins are currently among the most commonly 
prescribed agents for the prevention of cardiovascular disease. It is well 
established that statins reduce cholesterol levels and prevent coronary heart 
disease. Moreover, evidence suggests that statins have additional properties such 
as endothelial protection via actions on the nitric oxide synthetase system as well 
as anti-oxidant, anti-inflammatory and anti-platelet effects. There is evidence that 
all these actions might have potential therapeutic implications not only in stroke, 
but also in various neurological disorders, such as AD, Parkinson's disease, 
multiple sclerosis and primary brain tumors. The authors stated that currently 
available data suggest that statins are safe and effective in the treatment of these 
neurological disorders, although more research and new data are needed.

A Cochrane systematic evidence review (McGuinness et al, 2010) identified trials 
of statins for dementia involving 748 participants, and found that "there is 
is insufficient evidence to recommend statins for the treatment of dementia." 
Analysis from the studies available, including 1 large RCT, indicate statins have no 
benefit on the outcome measures (Alzheimer's Disease Assessment Scale-
cognitive subscale (ADAS-Cog) or Mini Mental State Examination (MMSE)). The 
authors stated that we need to await full results from the CLASP (Cholesterol 
lowering agent to slow progression of AD) study before we can be certain.

A systematic evidence review in BMJ Clinical Evidence (Warner et al, 2008) found 
statins to be of "unknown effectiveness" in treating the cognitive symptoms of 
dementia (Alzheimer's, Lewy body, or vascular).

In a randomized, double-blind, placebo-controlled trial, Sano et al (2011) 
examined if simvastatin slows the progression of symptoms in patients with mild-to 
-moderate AD and normal lipid levels. Participants were randomly assigned to 
receive simvastatin, 20 mg/day, for 6 weeks then 40 mg per day for the remainder 
of 18 months or identical placebo. The primary outcome was the rate of change in 
the ADAS-Cog portion. Secondary outcomes measured clinical global change, 
cognition, function, and behavior. A total of 406 individuals were randomized: 204 
to simvastatin and 202 to placebo. Simvastatin lowered lipid levels but had no 
effect on change in ADAS-Cog score or the secondary outcome measures. There 
was no evidence of increased adverse events with simvastatin treatment. The 
authors concluded that simvastatin had no benefit on the progression of symptoms 
in individuals with mild-to-moderate AD despite significant lowering of cholesterol.

*Indomethacin:*

In a double-blind, randomized, placebo-controlled study, de Jong and colleagues
(2008) examined if treatment with the indomethacin slows cognitive decline in patients with AD. A total of 51 patients with mild-to-moderate AD were enrolled in this trial. Patients received 100 mg indomethacin or placebo daily for 12 months. Additionally, all patients received omeprazole. The primary outcome measure was the change from baseline after 1 year of treatment on ADAS-Cog. Secondary outcome measures included MMSE, CIBIC with caregiver input, ADAS-non-Cog, the Neuropsychiatric Inventory, and the Interview for Deterioration in Daily Life in Dementia. Considerable recruitment problems of participants were encountered, leading to an under-powered study. A total of 19 out of 25 patients in the placebo group; and a total of 19 out of 26 patients in the indomethacin group completed the study. The deterioration on the ADAS-Cog was less in the indomethacin group (7.8 +/- 7.6), than in the placebo group (9.3 +/- 10.0). However, this difference (1.5 points; CI -4.5 to 7.5) was not statistically significant, and neither was any of the secondary outcome measures. The authors concluded that the results of this study are inconclusive with respect to the hypothesis that indomethacin slows the progression of AD.

Huperzine A:

In a Cochrane review, Li et al (2008) stated that the degeneration of acetylcholine-containing neurons in the basal forebrain has been implicated in the symptoms of AD. Thus, cholinesterase inhibitors may block the degradation of acetylcholine, increasing the effectiveness of the remaining cholinergic neurons. Huperzine A is a competitive, reversible inhibitor of acetyl cholinesterase that has both central and peripheral activity with the ability to protect cells against hydrogen peroxide, beta-amyloid protein (or peptide), glutamate, ischemia and staurosporine-induced cytotoxicity and apoptosis. These properties might qualify huperzine A as a promising agent for treating dementia (including AD). These researchers assessed the safety and effectiveness of huperzine A for the treatment of patients with AD. A total of 6 trials (454 patients) met the inclusion criteria. The methodological quality of most included trials was not high. It was shown that compared to placebo, huperzine A had beneficial effects on the improvement of general cognitive function measured by MMSE (WMD 2.81; 95 % CI: 1.87 to 3.76; p < 0.00001) and ADAS-Cog at 6 weeks (WMD 1.91; 95 % CI: 1.27 to 2.55) and at 12 weeks (WMD 2.51; 95 % CI: 1.74 to 3.28), global clinical assessment measured by Clinical Dementia Rating (CDR) (WMD -0.80; 95 % CI: -0.95 to -0.65) and CIBIC-plus (OR 4.32, 95 % CI: 2.37 to 7.90), behavioral disturbance measured by ADAS-non-Cog at 6 weeks (WMD -1.33, 95 % CI: -2.12 to -0.54) and at 12 weeks (WMD -1.52, 95 % CI: -2.39 to -0.65), and functional performance measured by activities of daily living (WMD = -7.17; 95 % CI: -9.13 to -5.22; p < 0.00001). However, huperzine A was not superior to placebo in the improvement of general cognitive function measured by Hasegawa Dementia Scale (HDS) (WMD: 2.78; 95 % CI: -0.17 to 5.73, p = 0.06) and specific cognitive function measured by Weslher Memory Scale (WMS) (WMD = 6.64; 95 % CI: -3.22 to 16.50; p = 0.19). No data were available on QOL and caregiver burden. The adverse events of huperzine A were mild and there were no significant differences of adverse events between huperzine A groups and control groups. The authors concluded that huperzine A appears to have some beneficial effects on improvement of general cognitive function, global clinical status, behavioral...
disturbance and functional performance, with no obvious serious adverse events for patients with AD. However, only 1 study was of adequate quality and size. Thus, there is insufficient evidence to make any recommendation about its use. Rigorous design, randomized, multi-center, large-sample trials of huperzine A for AD are needed to further evaluate the effects.

In a multi-center, phase II clinical trial, Rafii et al (2011) evaluated the safety, tolerability, and efficacy of huperzine A in mild-to-moderate AD. A total of 210 subjects were randomized to receive placebo (n = 70) or huperzine A (200 μg BID [n = 70] or 400 μg BID [n = 70]), for at least 16 weeks, with 177 subjects completing the treatment phase. The primary analysis assessed the cognitive effects of huperzine A 200 μg BID (change in ADAS-Cog at week 16 at 200 μg BID compared to placebo). Secondary analyses assessed the effect of huperzine A 400 μg BID, as well as effect on other outcomes including MMSE, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale, Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) scale, and Neuropsychiatric Inventory (NPI). Huperzine A 200 μg BID did not influence change in ADAS-Cog at 16 weeks. In secondary analyses, huperzine A 400 μg BID showed a 2.27-point improvement in ADAS-Cog at 11 weeks versus 0.29-point decline in the placebo group (p = 0.001), and a 1.92-point improvement versus 0.34-point improvement in the placebo arm (p = 0.07) at week 16. Changes in clinical global impression of change, NPI, and activities of daily living were not significant at either dose. The authors concluded that the primary efficacy analysis did not show cognitive benefit with huperzine A 200 μg BID.

Naproxen and Celecoxib:

In a randomized, double-masked trial, the ADAPT Research Group (2008) evaluated the effects of naproxen sodium and celecoxib on cognitive function in older adults. Men and women aged 70 years and older with a family history of AD enrolled in this study; 2,117 of 2,528 enrolled had follow-up cognitive assessment. Patients were randomly assigned to receive celecoxib (200 mg twice-daily), naproxen sodium (220 mg twice-daily), or placebo in a ratio of 1:1:1.5, respectively. Seven tests of cognitive function and a global summary score were measured annually. Longitudinal analyses showed lower global summary scores over time for naproxen compared with placebo (-0.05 SDs; p = 0.02) and lower scores on the modified MMSE over time for both treatment groups compared with placebo (-0.33 points for celecoxib [p = 0.04] and -0.36 points for naproxen [p = 0.02]). Restriction of analyses to measures collected from persons without dementia attenuated the treatment group differences. Analyses limited to measures obtained while subjects were being issued study drugs produced results similar to the intention-to-treat analyses. The authors concluded that the use of naproxen or celecoxib did not improve cognitive function. Furthermore, there was weak evidence for a detrimental effect of naproxen.


Metal Protein Attenuating Compounds:
In a Cochrane review, Sampson and colleagues (2008) assessed the effectiveness of metal protein attenuating compounds for the treatment of cognitive impairment due to AD. Randomized double-blind trials in which treatment with clioquinol was administered to patients with AD in parallel group comparison with placebo are included. Three reviewers independently evaluated the quality of trials according to the Cochrane Collaboration Handbook. The primary outcome measures of interest were cognitive function (as measured by psychometric tests). The secondary outcome measures of interest were in the following areas: QOL, functional performance, effect on caregiver, safety and adverse effects, and death. There was one included trial of clioquinol compared with placebo in 36 patients. There was no statistically significant difference in cognition (as measured on the ADAS-Cog) between active treatment and placebo groups at 36 weeks. One subject in the active treatment group developed neurological symptoms (impaired visual acuity and color vision) that resolved on cessation of treatment and was thought to be possibly attributable to the drug. The authors concluded that there is an absence of evidence as to whether clioquinol has any positive clinical benefit for patients with AD, or whether the drug is safe. These researchers have some concerns regarding the quality of the study methodology, especially the randomization (subjects in the active treatment group had higher mean pre-morbid IQ as measured by the National Adult Reading Test (NART) and this may have biased the results), the secondary analyses of results stratified by baseline disease severity and whether the study was adequately powered for the analysis of the other data collected on zinc and copper levels.

**Intra-Nasal Insulin:**

In a pilot study, Reger et al (2008) tested the hypothesis that daily intra-nasal insulin treatment would facilitate cognition in patients with early AD or its prodrome, amnesic mild cognitive impairment. The proportion of verbal information retained after a delay period was the planned primary outcome measure. Secondary outcome measures included attention, caregiver rating of functional status, and plasma levels of insulin, glucose, beta amyloid, and cortisol. A total of 25 subjects were randomly assigned to receive either placebo (n = 12) or 20 IU b.i.d. intra-nasal insulin treatment (n = 13) using an electronic atomizer, and 24 subjects completed the study. Participants, caregivers, and all clinical evaluators were blinded to treatment assignment. Cognitive measures and blood were obtained at baseline and after 21 days of treatment. Fasting plasma glucose and insulin were unchanged with treatment. The insulin-treated group retained more verbal information after a delay compared with the placebo-assigned group (p = 0.0374). Insulin-treated subjects also showed improved attention (p = 0.0108) and functional status (p = 0.0410). Insulin treatment raised fasting plasma concentrations of the short form of the beta amyloid peptide (Abeta 40; p = 0.0471) without affecting the longer isoform (Abeta 42), resulting in an increased Abeta 40/42 ratio (p = 0.0207). The authors concluded that the findings of this study supported further investigation of the benefits of intra-nasal insulin for patients with AD, and suggested that intra-nasal peptide administration may be a novel approach to the treatment of neuro-degenerative disorders.

In a pilot study, Craft and colleagues (2012) examined the effects of intra-nasal
insulin administration on cognition, function, cerebral glucose metabolism, and CSF biomarkers in adults with amnestic mild cognitive impairment or AD. The intent-to-treat sample consisted of 104 adults with amnestic mild cognitive impairment (n = 64) or mild-to-moderate AD (n = 40). Participants received placebo (n = 30), 20 IU of insulin (n = 36), or 40 IU of insulin (n = 38) for 4 months, administered with a nasal drug delivery device (Kurve Technology, Bothell, WA). Primary outcome measures consisted of delayed story recall score and the Dementia Severity Rating Scale score, and secondary measures included the ADAS-cog score and the ADCS-ADL scale. A subset of participants underwent lumbar puncture (n = 23) and positron emission tomography with fludeoxyglucose F 18 (n = 40) before and after treatment. Outcome measures were analyzed using repeated-measures analysis of covariance. Treatment with 20 IU of insulin improved delayed memory (p < 0.05), and both doses of insulin (20 and 40 IU) preserved caregiver-rated functional ability (p < 0.01). Both insulin doses also preserved general cognition as assessed by the ADAS-cog score for younger participants and functional abilities as assessed by the ADCS-ADL scale for adults with AD (p < 0.05). Cerebrospinal fluid biomarkers did not change for insulin-treated participants as a group, but, in exploratory analyses, changes in memory and function were associated with changes in the Aβ42 level and in the tau protein-to-Aβ42 ratio in CSF. Placebo-assigned participants showed decreased fludeoxyglucose F 18 uptake in the parieto-temporal, frontal, pre-cuneus, and cuneus regions and insulin-minimized progression. No treatment-related severe adverse events occurred. The authors concluded that these findings support longer trials of intra-nasal insulin therapy for patients with amnestic mild cognitive impairment and patients with AD. Drawbacks of this study included the availability of data on biomarkers and brain metabolism for only a subset of patients, and the short duration of treatment.

**Continuous Drainage of Cerebral Spinal Fluid:**

Alzheimer’s disease has been associated with abnormal cerebral clearance of macromolecules such as amyloid and microtubule-associated-protein tau (MAP-tau). It has been hypothesized that improving clearance of macromolecules from the central nervous system (CNS) might slow the progression of dementia. In a prospective, randomized, double-blinded, placebo-controlled trial, Silverberg and co-workers (2008) evaluated the safety and effectiveness of a surgically implanted shunt in subjects with probable AD. A total of 215 subjects with probable AD received either a low-flow ventriculo-peritoneal shunt or a sham (occluded) shunt for 9 months. Longitudinal CSF sampling was performed in both active and control subjects. Primary outcome measures were the Mattis Dementia Rating Scale and the Global Deterioration Scale. Cerebral spinal fluid Abeta (1-42) and MAP-tau also were assayed. After a planned interim analysis, the study was halted for futility. Using the intent-to-treat population, no between-group differences were observed in the primary outcome measures. The surgical procedure and device were associated with 12 CNS infections, some temporally associated with CSF sampling. All were treated successfully. The authors concluded that there is no benefit to low-flow CSF shunting in subjects with mild-to-severe AD. Cerebral spinal fluid infections, while treatable, occurred more frequently than expected, in some cases likely related to CSF sampling.

**Transcranial Direct Current Stimulation:**
In a preliminary study, Ferrucci and colleagues (2008) assessed the cognitive effect of transcranial direct current stimulation (tDCS) over the temporo-parietal areas in patients with AD. In 10 patients with probable AD, anodal tDCS (AtDCS), cathodal tDCS (CtDCS), and sham tDCS (StDCS) were delivered over the temporo-parietal areas in 3 sessions. In each session recognition memory and visual attention were tested at baseline (pre-stimulation) and 30 minutes after tDCS ended (post-stimulation). After AtDCS, accuracy of the word recognition memory task increased (pre-stimulation: 15.5 +/- 0.9, post-stimulation: 17.9 +/- 0.8, p = 0.0068) whereas after CtDCS it decreased (15.8 +/- 0.6 versus 13.2 +/- 0.9, p = 0.011) and after StDCS it remained unchanged (16.3 +/- 0.7 versus 16.0 +/- 1.0, p = 0.75). Transcranial direct current stimulation left the visual attention-reaction times unchanged. The authors concluded that tDCS delivered over the temporo-parietal areas can specifically affect a recognition memory performance in patients with AD. They noted that their finding prompted studies using repeated tDCS, in conjunction with other therapeutic interventions for treating patients with AD. The drawbacks of this study were: (i) only one kind of memory was tested, (ii) the duration of the effects induced by a single tDCS was unexamined, and (iii) the effects, if any, of the elicited memory changes on patients' daily life were unclear.

Vaccine Therapy:

Okura and Matsumoto (2008) noted that clinical trials of active vaccine for AD were halted as a consequence of the development of meningoencephalitis in some patients. However, vaccine therapy is thought to be effective based on the clinical and pathological findings of the vaccinated patients. Based on this information, active and passive vaccines have been developed, some of which are now undergoing clinical trials in Europe and the United States. However, there are still some problems for general application of such drugs for patients with AD. Salloway and Correia (2009) stated that in the active vaccine approach, a small fragment of beta-amyloid is injected to stimulate the production of beta amyloid antibodies to lower brain amyloid levels. However, although active vaccines are designed primarily to stimulate a B-cell response, they can cause adverse effects via unplanned stimulation of T-cells. Thus, passive immunization with a monoclonal antibody against beta amyloid may be a safer approach; and several compounds are undergoing clinical trials.

Stem Cell Therapy:

Alzheimer's disease is characterized by degeneration and dysfunction of synapses and neurons in brain regions that are critical for learning as well as memory functions. The endogenous generation of new neurons in certain areas of the mature brain, derived from neural stem cells, has raised hope that stem cells may be employed for structural brain repair. Stem cell therapy has been suggested as a possible strategy for replacing damaged circuitry and restoring learning and memory abilities in patients with AD (Feng et al, 2009). However, there is a lack of evidence regarding the effectiveness of this approach.

Bapineuzumab:

In a phase II clinical trial, Salloway and colleagues (2009) examined the effectiveness of bapineuzumab, a humanized anti-amyloid-beta (Abeta)
monoclonal antibody, for the potential treatment of AD. The study enrolled 234 patients, randomly assigned to intravenous bapineuzumab or placebo in 4 dose cohorts (0.15, 0.5, 1.0, or 2.0 mg/kg). Patients received 6 infusions, 13 weeks apart, with final assessments at week 78. The pre-specified primary efficacy analysis in the modified intent-to-treat population assumed linear decline and compared treatment differences within dose cohorts on the Alzheimer's Disease Assessment Scale-Cognitive and Disability Assessment for Dementia. Exploratory analyses combined dose cohorts and did not assume a specific pattern of decline. No significant differences were found in the primary efficacy analysis. Exploratory analyses showed potential treatment differences (p < 0.05, unadjusted for multiple comparisons) on cognitive and functional endpoints in study "completers" and apolipoprotein E (APOE) epsilon4 non-carriers. Reversible vasogenic edema, detected on brain MRI in 12/124 (9.7 %) bapineuzumab-treated patients, was more frequent in higher dose groups and APOE epsilon4 carriers. Six vasogenic edema patients were asymptomatic; 6 experienced transient symptoms. The authors concluded that primary efficacy outcomes in this phase II trial were not significant. Potential treatment differences in the exploratory analyses support further investigation of bapineuzumab in phase III with special attention to APOE epsilon4 carrier status. Due to varying doses and a lack of statistical precision, this Class II ascending dose trial provided insufficient evidence to support or refute a benefit of bapineuzumab.

Kerchner and Boxer (2010) stated that bapineuzumab appears capable of reducing the cerebral beta-amyloid peptide burden in patients with AD. However, particularly in APOE 4 carriers, its ability to slow disease progression remains uncertain, and vasogenic edema, a dose-limiting and potentially severe adverse reaction, may limit its clinical applicability.

Salloway et al (2014) conducted 2 double-blind, randomized, placebo-controlled, phase III trials involving patients with mild-to-moderate AD -- one involving 1,121 carriers of the APOE epsilon4 allele and the other involving 1,331 non-carriers. Bapineuzumab or placebo, with doses varying by study, was administered by intravenous infusion every 13 weeks for 78 weeks. The primary outcome measures were scores on 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11), with scores ranging from 0 to 70 and higher scores indicating greater impairment and the Disability Assessment for Dementia (DAD, with scores ranging from 0 to 100 and higher scores indicating less impairment). A total of 1,090 carriers and 1,114 non-carriers were included in the efficacy analysis. Secondary outcome measures included findings on positron-emission tomographic amyloid imaging with the use of Pittsburgh compound B (PIB-PET) and CSF phosphorylated tau (phospho-tau) concentrations. There were no significant between-group differences in the primary outcomes. At week 78, the between-group differences in the change from baseline in the ADAS-cog11 and DAD scores (bapineuzumab group minus placebo group) were -0.2 (p = 0.80) and -1.2 (p = 0.34), respectively, in the carrier study; the corresponding differences in the non-carrier study were -0.3 (p = 0.64) and 2.8 (p = 0.07) with the 0.5 mg/kg dose of bapineuzumab and 0.4 (p = 0.62) and 0.9 (p = 0.55) with the 1.0 mg/kg dose. The major safety finding was amyloid-related imaging abnormalities with edema among patients receiving bapineuzumab, which increased with bapineuzumab dose and APOE epsilon4 allele number and which led to discontinuation of
the 2.0 mg/kg dose. Between-group differences were observed with respect to PIB-PET and CSF phospho-tau concentrations in APOE ε4 allele carriers but not in non-carriers. The authors concluded that bapineuzumab did not improve clinical outcomes in patients with AD, despite treatment differences in biomarkers observed in APOE ε4 carriers.

**Etanercept:**

Tobinick (2009) stated that tumor necrosis factor (TNF) is an immune signalling molecule produced by glia, neurons, macrophages and other immune cells. In the brain, among other functions, TNF serves as a gliotransmitter, secreted by glial cells that envelope and surround synapses, which regulates synaptic communication between neurons. The role of TNF as a gliotransmitter may help explain the profound synaptic effects of TNF that have been demonstrated in the hippocampus, in the spinal cord and in a variety of experimental models. Excess TNF is present in the CSF of individuals with AD, and has been implicated as a mediator of the synaptic dysfunction that is hypothesized to play a central role in the pathogenesis of AD. Tumor necrosis factor may also play a role in endothelial and microvascular dysfunction in AD, and in amyloidogenesis and amyloid-induced memory dysfunction in AD. Genetic and epidemiological evidence has implicated increased TNF production as a risk factor for AD. Peri-spinal administration of etanercept produced sustained clinical improvement in a 6-month, open-label pilot study in patients with AD ranging from mild to severe. Subsequent case studies have documented rapid clinical improvement following peri-spinal etanercept in both AD and primary progressive aphasia, providing evidence of rapidly reversible, TNF-dependent, pathophysiological mechanisms in AD and related disorders. The author state that peri-spinal etanercept for AD merits further study in randomized clinical trials.

Andrade and Radhakrishnan (2009) stated that experimental treatments potentially useful for AD include dimebon (an anti-inflammatory agent), PBT2 (a metal-protein attenuating compound) and etanercept; the safety and effectiveness of the Alzheimer's vaccine remains to be proven, and growth hormone secretagogue and tarenflurbil (a gamma-secretase inhibitor) are likely ineffective.

**Applied Behavior Analysis:**

Bakke (1997) noted that while psychoactive drugs are the usual treatment choice for problem behaviors in individuals with AD, non-drug treatments are increasingly sought. This investigator described applied behavior analysis, the predominant non-drug treatment approach for behavior problems in people with cognitive impairments associated with developmental disabilities. Applied behavior analysis identifies the causes of an individual's problem behavior through "functional assessment" and then employs treatment methods that address those causes. Functional assessment seeks information on environmental and internal factors influencing a problem behavior, emphasizing the function or purpose the problem behavior serves for the individual. The author concluded that applied behavior analysis merits further investigation as a treatment approach to behavior problems in AD. Furthermore, in a review on the etiology and management of psychiatric and behavioral symptoms in AD and other dementias, Aarsland et al (2005) stated that more studies are needed to clarify the role of cholinergic and other
psychotropic agents as well as non-pharmacologic interventions for psychiatric and behavioral symptoms in patients with dementia. Also, in a review on AD, Ballard et al (2011) did not mention the use of applied behavior analysis for the treatment of neuropsychiatric symptoms in AD patients.

**Beta-Amyloid Degrading Enzymes:**

Miners and colleagues (2011) stated that there is increasing evidence that deficient clearance of β-amyloid (Aβ) contributes to its accumulation in late-onset AD. Several Aβ-degrading enzymes, including neprilysin (NEP), insulin-degrading enzyme, and endothelin-converting enzyme reduce Aβ levels and protect against cognitive impairment in mouse models of AD. The activity of several Aβ-degrading enzymes rises with age and increases still further in AD, perhaps as a physiological response to minimize the build-up of Aβ. The age- and disease-related changes in expression of more recently recognized Aβ-degrading enzymes (e.g. NEP-2 and cathepsin B) remain to be investigated, and there is strong evidence that reduced NEP activity contributes to the development of cerebral amyloid angiopathy. Regardless of the role of Aβ-degrading enzymes in the development of AD, experimental data indicate that increasing the activity of these enzymes (NEP in particular) has therapeutic potential in AD, although targeting their delivery to the brain remains a major challenge. The most promising current approaches include the peripheral administration of agents that enhance the activity of Aβ-degrading enzymes and the direct intra-cerebral delivery of NEP by convection-enhanced delivery. In the longer term, genetic approaches to increasing the intra-cerebral expression of NEP or other Aβ-degrading enzymes may offer advantages.

**Light Therapy:**

Nowak and Davis (2011) examined the effect as well as duration of effect of therapeutic light on sleep, rest-activity, and global function in women with AD using mixed methods in a 2-group experimental design with repeated measures on 1 factor. A total of 20 women with AD were randomized to experimental or control conditions. Blue-green or dim red light was delivered via cap visor in the morning. Results of the qualitative analysis of serial interviews with family and facility care-givers regarding perceived effect of light on global function were presented. Themes emerged in both groups with respect to cognition and psychosocial function. The authors concluded that future studies with larger samples using quantitative measures of global function are needed to verify these preliminary findings.

**Solanezumab:**

Solanezumab is a humanized monoclonal antibody that preferentially binds soluble forms of amyloid and in preclinical studies promoted its clearance from the brain. In 2 phase III, double-blind trials (EXPEDITION 1 and EXPEDITION 2), Doody and colleagues (2014) randomly assigned 1,012 and 1,040 patients, respectively, with mild-to-moderate AD to receive placebo or solanezumab (administered intravenously at a dose of 400 mg) every 4 weeks for 18 months. The primary outcomes were changes from baseline to week 80 in scores on (i) ADAS-cog11 (range of 0 to 70) with higher scores indicating greater cognitive impairment and (ii) the ADCS-ADL (range of 0 to 78) with lower scores indicating
worse functioning. After analysis of data from EXPEDITION 1, the primary outcome for EXPEDITION 2 was revised to the change in scores on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range of 0 to 90, with higher scores indicating greater impairment), in patients with mild AD. Neither study showed significant improvement in the primary outcomes. The modeled difference between groups (solanezumab group minus placebo group) in the change from baseline was -0.8 points for the ADAS-cog11 score (95 % CI: -2.1 to 0.5; p = 0.24) and -0.4 points for the ADCS-ADL score (95 % CI: -2.3 to 1.4; p = 0.64) in EXPEDITION 1 and -1.3 points (95 % CI: -2.5 to 0.3; p = 0.06) and 1.6 points (95 % CI: -0.2 to 3.3; p = 0.08), respectively, in EXPEDITION 2. Between-group differences in the changes in the ADAS-cog14 score were -1.7 points in patients with mild AD (95 % CI: -3.5 to 0.1; p = 0.06) and -1.5 in patients with moderate AD (95 % CI: -4.1 to 1.1; p = 0.26). In the combined safety data set, the incidence of amyloid-related imaging abnormalities with edema or hemorrhage was 0.9 % with solanezumab and 0.4 % with placebo for edema (p = 0.27) and 4.9 % and 5.6 %, respectively, for hemorrhage (p = 0.49). The authors concluded that solanezumab failed to improve cognition or functional ability.

**Plasma Exchange and Hemapheresis:**

Boada et al (2014) stated that there is a growing interest in new therapeutic strategies for the treatment of AD that focus on reducing the beta-amyloid peptide (Aβ) burden in the brain by sequestering plasma Aβ, a large proportion of which is bound to albumin and other proteins. These researchers discussed the concepts of interaction between Aβ and albumin that have given rise to AMBAR (Alzheimer's Disease Management by Albumin Replacement) project, a new multicenter, RCT for the treatment of AD. Results from preliminary research suggested that Albutein® (therapeutic albumin, Grifols) contains no quantifiable levels of Aβ. Studies also showed that Albutein® has Aβ binding capacity. On the other hand, AD entails a high level of nitro-oxidative stress associated with fibrillar aggregates of Aβ that can induce albumin modification, thus affecting its biological functions. Results from the phase II study confirmed that using therapeutic apheresis to replace endogenous albumin with Albutein® 5 % is feasible and safe in patients with AD. This process resulted in mobilization of Aβ and cognitive improvement in treated patients. The AMBAR study will test combination therapy with therapeutic apheresis and hemapheresis with the possible leverage effect of Albutein® with IVIG replacement (Flebogamma® DIF). Cognitive, functional, and behavioral changes in patients with mild-to-moderate AD will be assessed.
CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes not covered for indications listed in the CPB:

38232
38240
38241
38242
61863
+ 61864

61867
+ 61868
61880
61885
+ 62160
62180 - 62258
63740 - 63746
64553
90281 - 90283
99183
95974
+ 95975
95978
+ 95979
98960

HCPCS codes not covered for indications listed in the CPB:

A4575  Topical hyperbaric oxygen chamber, disposable
A4633  Replacement bulb/lamp for ultraviolet light therapy system, each
C1300  Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval
C1767  Generator, neurostimulator (implantable), non rechargeable
<table>
<thead>
<tr>
<th>Code</th>
<th>Item Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1778</td>
<td>Lead, neurostimulator (implantable)</td>
</tr>
<tr>
<td>C1816</td>
<td>Receiver and/or transmitter, neurostimulator (implantable)</td>
</tr>
<tr>
<td>E0203</td>
<td>Therapeutic lightbox, minimum 10,000 lux, table top model</td>
</tr>
<tr>
<td>E0446</td>
<td>Topical oxygen delivery system, not otherwise specified, includes all supplies and accessories</td>
</tr>
<tr>
<td>J0900</td>
<td>Injection, testosterone enanthate and estradiol valerate, up to 1cc</td>
</tr>
<tr>
<td>J1000</td>
<td>Injection, depo-estradiol cypionate, up to 5 mg</td>
</tr>
<tr>
<td>J1050</td>
<td>Injection, medroxyprogesterone acetate, 1 mg</td>
</tr>
<tr>
<td>J1060</td>
<td>Injection, testosterone cypionate and estradiol cypionate, up to 1 ml</td>
</tr>
<tr>
<td>J1380</td>
<td>Injection, estradiol valerate, up to 10 mg</td>
</tr>
<tr>
<td>J1410</td>
<td>Injection, estrogen conjugated, per 25 mg</td>
</tr>
<tr>
<td>J1438</td>
<td>Injection, etanercept, 25 mg</td>
</tr>
<tr>
<td>J1459</td>
<td>Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin, (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1566</td>
<td>Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg</td>
</tr>
<tr>
<td>J1568</td>
<td>Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1572</td>
<td>Injection, immune globulin, (Flebogamma / Flebogamma Dif), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1950</td>
<td>Injection, leuprolide acetate (for depot suspension), per 3.75 mg</td>
</tr>
<tr>
<td>J9217</td>
<td>Leuprolide acetate (for depot suspension), 7.5 mg</td>
</tr>
<tr>
<td>J9218</td>
<td>Leuprolide acetate implant, 65 mg</td>
</tr>
<tr>
<td>J9219</td>
<td>Leuprolide acetate, per 1 mg</td>
</tr>
<tr>
<td>L8680</td>
<td>Implantable neurostimulator electrode, each</td>
</tr>
</tbody>
</table>
L8681 Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only

L8682 Implantable neurostimulator radiofrequency receiver

L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver

L8685 Implantable neurostimulator pulse generator, single array, rechargeable, includes extension

L8686 Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension

L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension

L8688 Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

L8695 External recharging system for battery (external) for use with implantable neurostimulator, replacement only

S0190 Mitopristone, oral, 200 mg

S2107 Adoptive immunotherapy i.e., development of specific anti-tumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment

**ICD-9 codes not covered for indications listed in the CPB:**

331.0 Alzheimer's disease
The above policy is based on the following references:
