Effective May 1, 2013 please refer to Pharmacy Policy

Name of Policy:
Repository Corticotropin Injection

Policy #: 316
Category: Pharmacology
Latest Review Date: May 2013
Policy Grade: Policy no longer scheduled for regular literature reviews and updates.

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:
1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:
1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Repository corticotropin intramuscular or subcutaneous injection is primarily used for treating infantile spasms (West syndrome). It has also been investigated for diagnostic testing of adrenocortical function and for treating a variety of other conditions.

Repository corticotropin injection (H.P. Acthar® Gel, Questcor, Union City, CA) is a purified, sterile preparation of the natural form of adrenocorticotrophic hormone (ACTH) in gelatin to provide a prolonged release after intramuscular or subcutaneous injection. ACTH works by stimulating the adrenal cortex to produce cortisol, corticosterone, and a number of other hormones.

According to the 2010 product information (product labeling), repository corticotropin injection may be used in the treatment of the following conditions:

1.1 Infantile spasms:
   Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.

1.2 Multiple Sclerosis:
   Treatment of acute exacerbations of multiple sclerosis in adults.

1.3 Rheumatic Disorders:
   Indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis, Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), Ankylosing spondylitis.

1.4 Collagen Diseases:
   During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).

1.5 Dermatologic Diseases:
   Indicated for treatment of severe erythema multiforme, Stevens-Johnson syndrome.

1.6 Allergic States:
   Serum sickness.

1.7 Ophthalmic Diseases:
   Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis; optic neuritis; chorioretinitis; anterior segment inflammation.

1.8 Respiratory Diseases:
   Symptomatic sarcoidosis

1.9 Edematous State:
   To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

Contraindications for use of this agent include scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin.

Unlike previous versions, the 2010 product label does not mention the use of repository corticotropin injection for diagnostic testing of adrenocortical function.
West Syndrome/Infantile Spasms
West syndrome is a rare epileptic disorder of early infancy (90% of cases are diagnosed the first year of life) consisting of three main characteristics; infantile spasm, mental retardation and hypsarrhythmia, a specific abnormal pattern on EEG. Often the term “infantile spasms” is used synonymously with West syndrome. Infantile spasms are characterized by an initial contraction phase followed by a more sustained tonic phase.

Other treatments for infantile spasms include:

Vigabatrin (Sabril®, Lundbeck, Inc.) oral solution is another available treatment for infantile spasms. Sabril is indicated as monotherapy for pediatric patients with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss.

Cosyntropin (Cortosyn®, Amphastar), a synthetic form of ACTH, is created by isolating the first 24 amino acids from ACTH peptide. Unlike the natural form of ACTH, which is given intramuscularly or subcutaneously, Cortosyn should only be given intravenously. A depot formulation of cosyntropin (Synacthen Depot) is not approved by the Food and Drug Administration (FDA) for treating infantile spasms. However, it is available through a compassionate-use program through the specialty pharmacy Caligor Rx in New York.

According to the manufacturer’s Web site, beginning in August 2007, H.P. Acthar Gel is only available through specialized pharmacy distribution (i.e., no longer available from traditional pharmaceutical wholesalers or retail pharmacies). As of August 2009, the specialty pharmacy exclusive distribution is unchanged.

Policy:
Effective for dates of service on or after August 1, 2011 and prior to May 1, 2013:
Repository corticotropin injection does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for use in diagnostic testing of adrenocortical function.

Repository corticotropin injection meets Blue Cross and Blue Shield of Alabama’s medical criteria for treatment of infantile spasms ICD-9 345.60 (West’s syndrome).

Use of repository corticotropin injection meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as treatment of FDA indications, when:
• There are medical contraindications or intolerance to corticosteroids not expected to occur with use of repository corticotropin injection; or
• Patient has not responded to treatment with corticosteroid therapy; and
  o The lack of response or worsening symptoms is clearly documented in the patient’s medical record.

Except as noted above, use of repository corticotropin injection does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for
conditions that are not responsive to corticosteroid therapy including, but not limited to, use in tobacco cessation, acute gout, and childhood epilepsy.

Effective for dates of service prior to August 1, 2011:

Repository corticotropin injection meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the following:

- Diagnostic testing of adrenocortical function; or
- Treatment of infantile spasms ICD-9 345.60 (West’s syndrome).

Except as noted above, use of repository corticotropin injection does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for:

- Treatment of steroid-response conditions; or
- Conditions not responsive to corticosteroid therapy including use in tobacco cessation, acute gout and childhood epilepsy.

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

Key Points:
This policy was originally created in 2008 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period December 2009 through March 2012. Following is a summary of the key literature to date:

Infantile spasms
Data for use of repository corticotropin injection was summarized in a 2004 practice parameter from the American Academy of Neurology. While this review concluded that repository corticotropin injection is “probably an effective agent in the short-term treatment of infantile spasms,” evidence for repository corticotropin injection was stronger than for any other pharmacologic agent. The report also indicates that there is insufficient evidence to determine whether oral corticosteroids are effective and that vigabatrin was possibly effective but that there are concerns about retinal toxicity. This report also notes that the impact of treatment of seizures/spasms on long-term patient outcomes is unknown.

In 2008, Hancock et al authored a Cochrane review to compare the effects of single drugs used to treat infantile spasms in terms of long-term psychomotor development, subsequent epilepsy, control of the spasms, and adverse effects. Eleven RCTs (n=514) were included and tested 8 different drugs. Overall, methodology of the studies was poor. No study assessed long-term psychomotor development or onset of other seizure types. The authors concluded that “We found
no single treatment to be proven to be more efficacious in treating infantile spasms than any of the others (other than vigabatrin in the treatment of infantile spasms in tuberous sclerosis in one underpowered study). Few studies considered psychomotor development or subsequent seizure rates as outcomes and none had long-term follow-up. Further trials with larger numbers of participants, and longer follow-up are required.”

Other notable conclusions of the Cochrane review are:

- The strongest evidence suggests that hormonal treatment (prednisone, tetracosactide (synthetic ACTH [cosyntropin]) and ACTH) leads to resolution of spasms faster and in more infants that does vigabatrin.
- Responses without subsequent relapse may be no different; that is, the percent of cases that remain seizure-free may be similar when recurrence of seizures is considered.
- There is a suggestion that prednisolone or tetracosactide (cosyntropin) might improve the long-term developmental outcomes compared to vigabatrin in infants not found to have an underlying cause of their infantile spasms.
- Vigabatrin may be the treatment of choice in infantile spasms related to tuberous sclerosis.
- The authors also noted that naturally occurring ACTH is not available in the U.K.

The Cochrane review summarizes data on the use of ACTH versus high-dose prednisolone that was part of one study by Lux in 2004; this component was nested within the comparison of vigabatrin with hormonal treatment. In this study, 19 of 25 patients (76%) treated with ACTH (40 to 60 U/alternate days) had cessation of spasms compared with 21 of 30 (70%) patients treated with prednisolone (40 to 60 mg/day); odds ratio 1.36 (confidence interval 0.41 to 4.53). The odds ratio for resolution of EEG abnormalities in those for whom it was measured was 3.20 (favoring ACTH) and the confidence interval was 0.49 to 20.81.

A review article by Gettig et al noted many of the same items as the Cochrane review. They note that the effect of ACTH on long-term developmental outcomes in patients with infantile spasms warrants further research; and that the preferred dose and duration of treatment of infantile spasms with ACTH cannot be determined from the current evidence. They also comment that some of the poorly reported studies do not explicitly distinguish between ACTH and cosyntropin and it cannot be determined which treatment study patients received (natural vs. synthetic ACTH). They note that in some countries (e.g., Japan) cosyntropin is used interchangeably with ACTH because of access issues. This review provided information on two large surveys performed by Child Neurology Societies in the U.S. and Japan. In the US survey reported in 1994, 88% of respondents used ACTH as initial therapy for infantile spasms with a dosage of 40 IU/day for one to two months and the choice of drug was not influenced by etiology. In the survey from Japan reported in 2000, treatment was influenced by etiology and the order of drug selection was pyridoxine, valproate, and synthetic ACTH. In a smaller survey in the U.K. (1996), the initial choice was influenced by etiology, and vigabatrin was most frequently used for initial therapy. In addition, this review also comments that cosyntropin (synthetic ACTH) may be preferred over ACTH in diagnosing adrenal insufficiency because cosyntropin takes significantly less time (less than one hour compared to overnight).
Other potential uses of repository corticotrophin injection:

Gout
Underwood et al conducted a systematic review examining the effectiveness of treatments for acute gout. The authors concluded that repository corticotropin injection may be equally effective as corticosteroids at reducing symptoms in patients with acute gout. The evidence included one randomized controlled trial (n=31) of repository corticotropin injection versus a corticosteroid. The study did not include adverse events (harms). This evidence was given a low-quality rating by the authors.

Janssens et al authored a Cochrane Review that examined the efficacy and safety of systemic corticosteroids in the treatment of acute gout in comparison with placebo, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, other active drugs, other therapies including repository corticotropin injection, or no therapy. Clinically relevant differences between the studied systemic corticosteroids and the comparator drugs were not found; important safety problems attributable to the used corticosteroids were not reported. The quality of the three studies identified was graded as very low to moderate. Statistical pooling of results was not possible. The authors concluded that “There is inconclusive evidence for the efficacy and effectiveness of systemic corticosteroids in the treatment of acute gout.”

A review article by Schlesinger discusses treatments for acute gout, emphasizing the use of repository corticotropin injection. The author notes that there are no formal guidelines for the treatment of acute gout and only a few randomized controlled trials (RCTs) have been conducted to evaluate the efficacy of the various treatments for acute gout. New research suggests that repository corticotropin injection acts peripherally by activation of the melanocortin type 3-receptor, and this could be responsible, at least in part, for its efficacy in acute gout. The author concludes that “Randomized, long term, prospective, placebo-controlled trials are needed to evaluate the therapeutic role of repository corticotropin injection versus NSAIDs (non steroidal anti-inflammatory drugs) and other treatment modalities, such as corticosteroids, in the treatment of acute gout.” Thus, some may not consider gout as a corticosteroid-responsive disease and may consider the use of repository corticotropin.

Childhood Epilepsy
Gayatri et al authored a Cochrane review to determine the efficacy of corticosteroids and repository corticotropin injection in terms of seizure control, improvements in cognition, quality of life, and tolerability compared to placebo or other antiepileptic drugs for the treatment of childhood epilepsy. (This report was on childhood epilepsy other than epileptic spasms.) All randomized controlled trials of administration of corticosteroids or repository corticotropin injection to children (younger than 16 years) with epilepsy were included. Outcomes included cessation of seizures, reduction in seizure frequency, and improvement in cognition, quality of life, and adverse effects. A single RCT was included that recruited five patients in a double-blind crossover trial. The authors concluded that “No evidence was found for the efficacy or safety of corticosteroids or repository corticotropin injection in treating childhood epilepsies. Clinicians using steroids in childhood epilepsies, other than for epileptic spasms, should take this into account before using these agents.”
Tobacco cessation
For potential use in tobacco cessation, one article described an uncontrolled study of its use in 15 patients.

Nephrotic syndrome
Bomback et al published a retrospective case series including all known patients treated with ACTH gel for idiopathic, nondiabetic nephritic syndrome in the United States outside of research settings through 2009; patients needed to have been treated for at least six months. Patients were identified obtained by contacting nephrologists referred to the researchers by Questor Pharmaceuticals. A total of 25 patients were identified; data were not available for 4 patients. Of the 21 remaining patients, ACTH gel was used as a primary therapy in 3; the other 18 patients had failed a mean of 2.3 immunosuppressive regimens before using ACTH gel. An additional 5 patients were identified who were treated for less than six months and were taken off therapy or lack of response; these patients were not included in the analysis. Four of the 21 (19%) patients were in complete remission, defined as stable or improved renal function with final proteinuria falling to less than 500 mg/day. An additional seven of 21 (33%) patients had a partial remission (at least a 50% reduction in proteinuria and final proteinuria 500 to 3500 mg/day). The study was retrospective, had a small sample size, did not have a control group and patient selection may have been biased.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received from three physician specialty societies and one academic medical center while this policy was under review for April 2010. In addition, unsolicited input was received from one foundation and three physicians. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was strong support for use of repository corticotropin in treatment of infantile spasms (West’s Syndrome).

Summary
While questions still exist about the role of repository corticotropin in the treatment of infantile spasms, this has been accepted as a treatment option and there is strong clinical support for this treatment. Thus, this use may be considered medically necessary. The evidence is insufficient to support the use of repository corticotropin injection in conditions not responsive to corticosteroid therapy (such as tobacco cessation, acute gout, childhood epilepsy) to improve the net health outcome. Repository corticotropin injection is considered not medically necessary for patients with these conditions because the clinical outcomes with use of this specific material have not been shown to be superior to other approaches, including synthetic ACTH (cosyntropin), yet repository corticotropin is generally more costly than these alternatives. In addition, use of repository corticotropin may be associated with more adverse effects.

Guidelines, Recommendations and Position Statements
In May 2004, the American Academy of Neurology; Child Neurology Society released, Practice Parameter: Medical Treatment of Infantile Spasms: Report of the American Academy of Neurology and the Child Neurology Society. The report states the following recommendations
for adrenocorticotropic (ACTH): “ACTH is probably effective for the short-term treatment of infantile spasms and in the resolution of hypsarrhythmia. There is insufficient evidence to recommend the optimum dosage and duration of treatment with ACTH for the treatment of infantile spasms.”

In 2010, an industry-sponsored Infantile Spasms Working Group published a consensus report on diagnosis and treatment of infantile spasms. Regarding treatment, the report concluded: “At this time, ACTH and VGB (vigabatrin) are the only drugs with proven efficacy to suppress clinical spasms and abolish the hypsarrhythmic EEG in a randomized clinical trial setting (Mackay et al., 2004) and thus remain first-line treatment.”

**Key Words:**
ACTH gel, Acthar gel, infantile spasms, West’s syndrome, repository corticotropin injection, Vigabatrin, Cosyntropin, Cortosyn®, Sabril®, Synacthen Depot, Adrenocorticotropic hormone, HP Acthar gel,

**Approved by Governing Bodies:**
Synacthen Depot is not approved by the Food and Drug Administration (FDA) for treating infantile spasms. However, it is available through a compassionate-use program through the specialty pharmacy Caligor Rx in New York.

In December 2008, Questcor resubmitted a supplemental new drug application (sNDA) for H.P. Acthar gel (repository corticotrophin) injection to the FDA for treating infantile spasms. Approval was granted in October 2010.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan.
Pre-certification requirements: Not applicable

**Coding:** HCPCS: J0800 Injection, corticotropin, up to 40 units

**References:**

**Policy History:**
Medical Policy Group, March 2008 (2)
Medical Policy Administration Committee, March 2008
Available for comment March 19-May 2, 2008
Medical Policy Group, October 2009 (1)
Medical Policy Administration Committee, November 2009
Available for comment November 6-December 21, 2009
Medical Policy Panel, December 2009
Medical Policy Panel, May 2011
Medical Policy Group, May 2011 (2) Policy change, Key Point and Reference update
Medical Policy Administration Group, June 2011
Available for comment June 17 – July 31, 2011
Medical Policy Panel May 2012
Medical Review Group, June 2012 (2): No literature found to change Policy Statement, Key Points, or References.
Medical Policy Group, May 2013: Effective May 1, 2013 Refer to Pharmacy Policy

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

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