Repository Corticotropin Injection

Policy Number: 5.01.17  Last Review: 05/2017
Origination: 03/2009  Next Review: 03/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for repository corticotropin injection ACTHAR gel when it is determined to be medically necessary because the following criteria have been met.

When Policy Topic is covered
Repository corticotropin injection may be considered medically necessary for treatment of infantile spasms (West syndrome).

Drug must be sourced from an approved specialty infusion provider.

When Policy Topic is not covered
Repository corticotropin injection is considered investigational for use in diagnostic testing of adrenocortical function.

Use of repository corticotropin injection is considered investigational as treatment of corticosteroid-responsive conditions, unless there are medical contraindications or intolerance to corticosteroids that are not also expected to occur with use of repository corticotropin injection.

Except as noted here, use of repository corticotropin injection 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.

Considerations
Repository corticotropin injection is one of the agents that can be considered for treatment of infantile spasms as noted in the Rationale section.

The product information material makes the following comments about dosage:

- In the treatment of infantile spasms, the recommended dose is 150 U/m2 divided into twice daily intramuscular injections of 75 U/m2. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period.
- In the treatment of other disorders and diseases, dosing will need to be individualized depending on the disease under treatment and the medical condition of the patient. It may be necessary to taper the dose.

Acthar gel should never be used intravenously.

This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy number 5.01.17.
Description of Procedure or Service
Repository corticotropin injection (H.P. Acthar® Gel, Questcor Pharmaceuticals/Mallinckrodt Pharmaceuticals, St. Louis, MO) is a purified, sterile preparation of the natural form of adrenocorticotropic hormone (ACTH) in gelatin to provide a prolonged release after intramuscular or subcutaneous injection. ACTH is produced and secreted by the pituitary gland; H.P. Acthar Gel uses ACTH obtained from porcine pituitaries. ACTH works by stimulating the adrenal cortex to produce cortisol, corticosterone, and a number of other hormones.

H.P. Acthar Gel was approved by the U.S. Food and Drug Administration (FDA) in 1952, before there was a requirement that companies provide clinical evidence of efficacy. The product label states that Acthar Gel is indicated for a number of conditions, as follow:

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

1.1 Infantile Spasms in infants and children younger than 2 years of age.
1.2 Multiple Sclerosis: Treatment of acute exacerbations of multiple sclerosis in adults (indication added in 1978).
1.3 Rheumatic Disorders: Adjunctive therapy for patients with acute episodes or exacerbations of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis.
1.4 Collagen Diseases: Treatment of selected cases of systemic lupus erythematosus and systemic dermatomyositis.
1.5 Dermatologic Diseases: Treatment of severe erythema multiforme and Stevens-Johnson syndrome.
1.6 Allergic States: Treatment of serum sickness.
1.7 Ophthalmic Diseases: Treatment of severe acute and chronic allergic and inflammatory processes including optic neuritis, keratitis and iritis.
1.8 Respiratory Diseases: Treatment of symptomatic sarcoidosis.
1.9 Edematous State: Treatment of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or due to lupus erythematosus.

Among these indications, repository corticotropin injection is best known for the treatment of infantile spasms. This is a rare epileptic disorder of infancy (90% of cases are diagnosed in the first year of life). When infantile spasms are accompanied by neurodevelopmental regression and electroencephalogram findings of hypsarrhythmia, the condition is known as West syndrome. Vigabatrin oral solution is another available treatment for infantile spasms.

A synthetic derivative of ACTH is commercially available outside of the United States (under the trade names Cortosyn and Synacthen) but is not approved by FDA for any of the conditions currently included in the H.P. Acthar Gel FDA-approved label. In addition, a depot formulation of ACTH (Synacthen Depot) is available through a compassionate-use program through the specialty pharmacy Caligor Rx in New York. In June 2013, Questcor Pharmaceuticals announced that they acquired the rights to market Synacthen in the United States, once FDA approval is obtained.

Diagnostic testing of adrenocortical function, known as the ACTH test, is typically done with synthetic ACTH. Synthetic ACTH products have been approved by FDA for this purpose. Unlike previous versions of the H.P. Acthar product label, an updated label issued in 2010, did not mention the use of repository corticotropin injection for diagnostic testing of adrenocortical function.

Repository corticotropin injection has potential adverse effects similar to those that occur with other steroid medications such as elevated blood pressure, decrease in bone density, new infections or activation of previous infection, and overproduction of cortisol, which can cause symptoms of Cushing syndrome.

Regulatory Status
In 1952, H.P. Acthar Gel (Questcor Pharmaceuticals) was approved by the U.S. Food and Drug
Administration. The product label states that Acthar Gel is indicated for 19 conditions, including infantile spasms. 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 of the product label, an updated label issued in 2010, did not include the use of repository corticotropin injection for diagnostic testing of adrenocortical function.

Rationale
This policy was originally created in 2008 and was updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through August 18, 2016. Following is a summary of the key literature to date.

Evidence that Acthar Gel (ie, ACTH) is a reasonable alternative to corticosteroid treatment requires controlled studies demonstrating superiority or noninferiority of ACTH to corticosteroids as first-line treatment, or controlled studies showing comparable efficacy of ACTH with fewer adverse effects. Randomized controlled studies are crucial to avoid noncomparability of treatment groups. Alternatively, for patients unable to tolerate corticosteroids, the most appropriate study design would be a controlled study comparing ACTH with placebo.

Infantile spasms
In 2013, Hancock et al published an updated Cochrane review on medication treatment of infantile spasms.2 The authors identified 18 randomized controlled trials (RCTs) investigating a total of 12 different medications. The overall quality of studies was deemed to be poor (ie, fewer than half of the studies reported the method of randomization, and only 2 had more than 100 participants). A total of 5 studies compared treatment with adrenocorticotropic hormone (ACTH) with another medication. The review authors did not differentiate between synthetic and natural forms of ACTH. Two studies compared ACTH with vigabatrin (total sample sizes 9 and 42, respectively), 2 compared ACTH to prednisone (n=29 and 24, respectively), and 1 study with 52 participants compared ACTH with nitrazepam. A sixth study compared vigabatrin and ACTH in a subset of patients. Dosages and treatment regimens varied. The authors conducted several quantitative meta-analyses. A pooled analysis of 3 studies found that symptom resolution occurred in 30 of 45 patients (67%) responding to vigabatrin and 40 of 49 patients (82%) responding to ACTH. The difference between groups was statistically significant (odds ratio, 0.38; 95% confidence interval, 0.15 to 0.99). The authors noted that the limited evidence from RCTs suggests that hormonal treatment (prednisolone, tetracosactide depot and ACTH) resolves infantile spasms faster than vigabatrin and resolves the condition in more children, but long-term developmental and epilepsy outcomes are unknown.

Since the Cochrane review, in 2014, a RCT was published that assigned children with previously untreated infantile spasms to treatment with 40 to 60 IU synthetic ACTH every other day or 40 to 60 mg/day of oral prednisolone.3 The study was conducted in Sri Lanka and uses a form of ACTH that is not approved by the U.S. Food and Drug Administration for this indication. The primary outcome, assessed in a blinded fashion after a 14-day treatment period, was change in a hypsarrhythmia severity scale (possible score range, 0-16). Hypsarrhythmia is an abnormal interictal pattern seen on an electroencephalogram and can be considered an intermediate outcome; clinical outcomes such as symptom resolution were not assessed. Ninety-two children were randomized, and follow-up data were available on 80 (82%) of them. Mean improvement in the hypsarrhythmia score was 7.95 (SD=2.76) in the prednisolone arm and 6.00 (SD=2.61) in the ACTH arm. The between-group difference was significantly different (p<0.01), favoring treatment with prednisolone. Rates of adverse effects were similar in the 2 groups. This study suggests that prednisolone may at least be as effective as synthetic ACTH for treatment of infantile spasms. However, the study has methodologic limitations including a dropout rate of over 20%, lack of intention-to-treat analysis, short-term follow-up only, and use of intermediate outcomes.

Corticosteroid-Responsive Conditions
The product label for H.P. Acthar Gel (ie, ACTH) lists a number of corticosteroid-responsive conditions as indications for repository corticotropin injection, including rheumatoid arthritis, dermatomyositis, symptomatic sarcoidosis, nephrotic syndrome, multiple sclerosis (MS) exacerbations, and serum sickness. The only controlled studies found were for the treatment of MS (ie, not for other indications). Several RCTs published in the 1960s and early 1970s compared ACTH with placebo for the treatment of acute exacerbations of MS. A study described in recent review articles as the most rigorous of these RCTs was published by Rose et al.4,5 This was a multicenter, double-blind study that included 197 patients. Patients were randomized to receive intramuscular injections of ACTH gel or placebo during a 2- week hospitalization for acute exacerbations of MS. The study used Depo-ACTH and placebo, both prepared by the Upjohn Company. Review articles report that the study found that ACTH hastened improvement in symptoms but that the differences between the ACTH and placebo-treated patients were less marked as the dosage of ACTH was reduced during the second week of treatment.6

Use of ACTH for treating MS exacerbations decreased in the 1980s as intravenous (IV) corticosteroid treatment became more common. Two RCTs published in the late 1980s compared ACTH with IV corticosteroids. A study by Milanese et al with 30 patients found that dexamethasone was more effective than ACTH in shortening the length of the exacerbation.7 Thompson et al published a study that included 61 patients and compared ACTH and high-dose IV methylprednisolone.8 The authors did not find a statistically significant difference in the efficacy of the 2 treatments. The study was powered to detect a 1-point difference between the 2 groups on the Kurtzke function and disability scales. The scores before and after treatment were not reported.

There are also a limited number of small case series reporting on use of ACTH for other corticosteroidresponsive conditions. For example, in 2011, Bomback et al published a retrospective case series in 21 patients with idiopathic, nondiabetic nephrotic syndrome who were treated with ACTH gel. ACTH gel was used as a primary therapy in 3 patients; the other 18 patients had failed a mean of 2.3 immunosuppressive regimens before using ACTH gel.9 An additional 5 patients were identified who were retreated for less than 6 months and were taken off therapy for 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/d. An additional 7 of 21 (33%) patients had a partial remission (at least a 50% reduction in proteinuria and final proteinuria 500-3500 mg/d).

**Diagnostic Testing of Adrenocortical Function**

Diagnostic testing of adrenocortical function is typically done with synthetic ACTH. Studies have evaluated the value of synthetic ACTH for diagnosing adrenal insufficiency. For example, a 2008 meta-analysis identified 13 studies comparing low- and high-dose corticotropin tests for diagnosing adrenal insufficiency.10 A comparable literature base was not identified for use of H.P. Acthar gel used in the diagnostic testing of adrenocortical function, and no studies were found that compared synthetic ACTH and Acthar gel for this purpose.

**Non-Corticosteroid-Responsive Conditions**

Repository corticotropin injection has also been proposed for several off-label non-corticosteroidresponsive conditions including tobacco cessation, acute gout, and childhood epilepsy. Controlled studies were identified only for treatment of acute gout. In 2008, Janssens et al published 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, colchicine, other active drugs, other therapies including repository corticotropin injection, or no therapy.11 Three head-to-head trials were identified; one of these compared systemic corticosteroids with oral indomethacine and intramuscular ACTH. The quality of the 3 studies identified was graded as very low to moderate. None of the studies found clinically relevant differences between the studied systemic corticosteroids and the comparator drugs and important safety problems attributable to the used corticosteroids were not reported. The authors concluded that “There is inconclusive evidence for the efficacy and effectiveness of systemic corticosteroids in the treatment of acute gout.”

Billing Coding/Physician Documentation Information

J0800 Injection, corticotrophin, up to 40 units
96372 CPT Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
G40.401- G40.409 ICD10 Other Generalized epilepsy and epileptic syndromes, not intractable code range

Additional Policy Key Words
5.01.17

Policy Implementation/Update Information

03/2009 New policy
03/2010 Policy Revised: Policy updated with literature search January 2008 to August 2009; title “repository corticotropin injection” replacing “ACTH gel”; acute gout and childhood epilepsy added as investigational conditions; other policy statements unchanged; reference numbers 7-11 added
03/2012 Policy updated with literature review. Rationale extensively rewritten. References 1, 10 and 11 added; other references renumbered or removed. Policy statements unchanged.
Information about dosing in multiple sclerosis removed from Policy Guidelines.

03/2013  Reviewed – no changes recommended
03/2014  Reviewed – no changes recommended
03/2015  Policy updated; added Repository corticotropin injection is considered not medically necessary for use in diagnostic testing of adrenocortical function
03/2016  Policy updated with literature review; policies changed to investigational
03/2017  Policy updated with literature review; no changes to policy statement
05/2017  Add specialty infusion provider requirement

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