Repository corticotropin injection may be considered **medically necessary** for the treatment of infantile spasms (West syndrome).

Use of repository corticotropin injection is considered **investigational** as a treatment of corticosteroid-responsive conditions (see Policy Guidelines section).

Repository corticotropin injection is considered **investigational** for use in diagnostic testing of adrenocortical function.

Except as noted above, 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.

**POLICY GUIDELINES**

Some patients may have medical contraindications or intolerance to corticosteroids that are not expected to occur with use of repository corticotropin injection, and who therefore may benefit from repository corticotropin injections. This situation is not common.

Product information makes the following comments about dosage of H.P. Acthar® Gel for treatment of infantile spasms:

- 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).

H.P. Acthar® gel is used for intramuscular or subcutaneous injection and should never be used intravenously.
BENEFIT APPLICATION

BLUECARD/NATIONAL ACCOUNT ISSUES
State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

According to the manufacturer’s website, beginning in 2007, H.P. Acthar® Gel is only available through specialized pharmacy distribution (ie, it is no longer available from traditional pharmaceutical wholesalers or retail pharmacies).

BACKGROUND

REPOSITORY CORTICOTROPIN INJECTION
Repository corticotropin injection (H.P. Acthar Gel) 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.

REGULATORY STATUS
In 1952, H.P. Acthar® Gel (Questcor Pharmaceuticals/Mallinckrodt Pharmaceuticals, St. Louis, MO) was approved by the U.S. Food and Drug Administration (FDA). The original product label included at least 19 separate conditions, including infantile spasms. At one time, this product was indicated as an injection for diagnostic testing of adrenocortical function. In 2010, this indication was removed with an update to the product label.

Indications
H.P. Acthar Gel was approved by FDA before the requirement that companies provide evidence of clinical efficacy. The current prescribing indications and usage for Acthar® Gel are summarized in Table 1.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Populations or Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile spasms</td>
<td>Monotherapy for infants and children &lt;2 years of age</td>
</tr>
<tr>
<td>Multiple sclerosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Acute exacerbations of multiple sclerosis in adults</td>
</tr>
<tr>
<td>Rheumatic disorders</td>
<td>Adjunctive therapy for short term administration for acute episodes or exacerbations of psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis</td>
</tr>
<tr>
<td>Collagen diseases</td>
<td>During an exacerbation or as maintenance therapy in select cases of systemic lupus erythematosus and systemic dermatomyositis</td>
</tr>
<tr>
<td>Dermatologic diseases</td>
<td>Severe erythema multiforme and Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Allergic states</td>
<td>Serum sickness</td>
</tr>
<tr>
<td>Ophthalmic diseases&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Severe acute and chronic allergic and inflammatory processes</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>Symptomatic sarcoidosis</td>
</tr>
<tr>
<td>Edematous state&lt;sup&gt;c&lt;/sup&gt;</td>
<td>To induce a diuresis or a remission of proteinuria in the nephrotic syndrome</td>
</tr>
</tbody>
</table>

<sup>a</sup> According to the manufacturer's website, beginning in 2007, H.P. Acthar® Gel is only available through specialized pharmacy distribution.

<sup>b</sup> Severe acute and chronic allergic and inflammatory processes include severe acute and chronic urticaria, angioedema, and rhinoconjunctivitis.

<sup>c</sup> To induce a diuresis or a remission of proteinuria in the nephrotic syndrome.
Controlled clinical trials have shown H.P. Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease. Keratitis; iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis; anterior segment inflammation. Without uremia of the idiopathic type or due to lupus erythematosus.

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

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.

Adverse Events
Contraindications for the 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.

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

RATIONALE
This evidence review was created in February 2008 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through August 28, 2017.

Evidence that repository corticotropin injection (ie, natural adrenocorticotropic hormone [ACTH] injection) is a reasonable alternative to corticosteroid treatment requires controlled studies demonstrating superiority or noninferiority of repository corticotropin injection to corticosteroids as first-line treatment, or controlled studies showing comparable efficacy of with fewer adverse effects. Randomized controlled trials (RCTs) 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 repository corticotropin injection with placebo. The following is a summary of the key literature to date.

INFANTILE SPASMS
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 treatment available for infantile spasms.

A 2013 Cochrane review addressed medication treatment of infantile spasms, including ACTH. Reviewers identified 18 RCTs investigating 12 different medications. The studies were deemed to be of
poor quality, with more than half of them failing to report the method of randomization—and nearly all of them consisted of fewer than 100 participants. Five studies compared treatment with ACTH to another medication. Three trials assessed on natural ACTH and the others evaluated synthetic ACTH. Reviewers conducted several quantitative meta-analyses that did not differentiate between natural and synthetic ACTH. A pooled analysis of 3 studies found that symptom resolution occurred in 30 (67%) of 45 patients responding to vigabatrin and 40 (82%) of 49 patients responding to ACTH. The difference between groups was statistically significant (odds ratio, 0.38; 95% confidence interval, 0.15 to 0.99). Reviewers noted that the limited evidence from RCTs suggested that hormonal treatment (prednisolone, tetracosactide depot, ACTH) resolved infantile spasms faster than vigabatrin and resolved the condition in more children, but long-term developmental and epilepsy outcomes are unknown.

In addition to the RCTs cited by the Cochrane review, findings from a prospective national database of children with infantile spasms were published by Knupp et al in 2016. A total of 230 infants were included in the database, and 94 responded to initial treatment for infantile spasms. Response rates by type of treatment were 55 (55%) for ACTH, 21 (39%) for oral corticosteroids, 17 (36%) for vigabatrin, and 2 (9%) for “other” (p<0.001). The type of ACTH, natural or synthetic, was not specified and the groups may have differed on characteristics that affect outcomes. Some significant differences between groups were identified (eg, length of time from diagnosis to the start of treatment, history of prior seizures). In logistic regression models controlling for some potential confounding factors, children on ACTH remained more likely to respond to treatment than other children. However, there might have been residual confounding on unmeasured characteristics.

**Section Summary: Infantile Spasms**

There is some evidence from several RCTs and a prospective database that natural and synthetic ACTH have greater short-term efficacy in resolving infantile spasms than other medications (eg, vigabatrin, oral corticosteroids). However, most of the RCTs were small or of poor quality, and only a few evaluated natural ACTH.

**CORTICOSTEROID-RESPONSIVE CONDITIONS**

Controlled studies were identified for treatment of multiple sclerosis with ACTH, but not treatment of other corticosteroid-responsive conditions. Several RCTs, published in the 1960s and early 1970s, compared ACTH with placebo for the treatment of acute exacerbations of multiple sclerosis. A study described in recent review articles as the most rigorous of these RCTs was published by Rose et al in 1969 and 1970. This multicenter, double-blind study included 197 patients. Patients were randomized to intramuscular injections of ACTH gel or placebo during a 2-week hospitalization for acute exacerbations of multiple sclerosis. The trial used Depo-ACTH and placebo, both prepared by Upjohn. A 2013 review article 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.

Use of ACTH for treating multiple sclerosis 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 (1989) with 30 patients found that dexamethasone was more effective than ACTH in shortening the length of the exacerbation. Thompson et al (1989) published a study that included 61 patients and compared ACTH with high-dose IV methylprednisolone. The authors did not find a statistically significant difference in the efficacy of the 2 treatments.

There are also a limited number of small case series reporting on use of ACTH for other corticosteroid-responsive conditions. For example, in 2011, Bomback et al published a retrospective case series in 21 patients with idiopathic, non-diabetic 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. An additional 5 patients were identified who were treated for less than 6 months and were taken off therapy for lack of response; these patients were not included in the analysis. Four (19%) of the 21 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 (33%) of 21 patients had a partial remission (at least a 50% reduction in proteinuria and final proteinuria 500-3500 mg/d).

Section Summary: Corticosteroid-Responsive Conditions
There is insufficient evidence that ACTH gel is at least as effective as IV corticosteroids for the treatment of multiple sclerosis. One of the RCTs found that corticosteroids were more effective and the other found no significant difference in efficacy. There is a lack of evidence from controlled studies that ACTH is an effective treatment of other corticosteroid-responsive conditions.

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

Section Summary: Testing Adrenocortical Function
No studies were identified that evaluated repository corticotropin injection, or compared natural with synthetic ACTH, for diagnostic testing of adrenocortical function.

NON-CORTICOSTEROID-RESPONSIVE CONDITIONS
Repository corticotropin injection has been proposed for several off-label non-corticosteroid-responsive 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 compared the efficacy and safety of systemic corticosteroids in the treatment of acute gout 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 compared systemic corticosteroids with oral indomethacin and intramuscular ACTH. The quality of the 3 studies identified was graded as very low to moderate. None found clinically relevant differences between the systemic corticosteroids and the comparator drugs, and important safety problems attributable to the used corticosteroids were not reported. Reviewers concluded that “There is inconclusive evidence for the efficacy and effectiveness of systemic corticosteroids in the treatment of acute gout.”

Section Summary: Non-Corticosteroid-Responsive Conditions
There is a lack of controlled studies on ACTH for treatment of non-corticosteroid-responsive conditions, with the exception of gout. A Cochrane review identified a single trial comparing ACTH and systemic corticosteroids and this trial did not report clinically relevant differences in outcomes.

SUMMARY OF EVIDENCE
For individuals who have infantile spasms who receive repository corticotropin injection, the evidence includes RCTs, a systematic review, and a prospective cohort study. Relevant outcomes are symptoms and change in disease status. The systematic review judged the overall quality of the studies to be poor, with fewer than half reporting method of randomization and most assessing relatively few patients.
There was heterogeneity across studies and either vigabatrin or prednisolone was used as comparators. Multivariate analysis of a prospective cohort study found that children with infantile spasms who were treated with ACTH were more likely to respond than other children. However, the analysis might have been subject to residual confounding on unmeasured characteristics; further, the study did not differentiate between synthetic and natural ACTH. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have corticosteroid-responsive conditions (eg, rheumatoid arthritis, dermatomyositis, sarcoidosis, nephrotic syndrome, multiple sclerosis, serum sickness) who receive repository corticotropin injection, the evidence includes RCTs and small cases series. Relevant outcomes are symptoms and change in disease status. Overall, more recent studies evaluating multiple sclerosis have demonstrated that intravenous corticosteroids are at least as effective, or more effective, than repository corticotropin. Most studies assessing nephrotic syndrome have been small retrospective case studies. Ongoing studies are being conducted. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who need diagnostic testing of adrenal function who receive testing with repository corticotropin injection, the evidence does not include studies that compare its diagnostic accuracy with ACTH. Relevant outcomes are test accuracy and validity and other test performance measures. The lack of published evidence precludes conclusions on the validity of using repository corticotropin as a diagnostic test for adrenal function. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have non-corticosteroid-responsive conditions (eg, tobacco cessation, childhood epilepsy, acute gout) who receive repository corticotropin injection, the evidence includes 3 head-to-head trials identified for use in gout. Relevant outcomes are symptoms and change in disease status. The quality of these studies was deemed very low to moderate because there were no direct placebo-controlled trials and there were no clinically relevant differences found between drugs studied. The evidence is insufficient to determine the effects of the technology on health outcomes.

**SUPPLEMENTAL INFORMATION**

**CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS**

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.

In response to requests, input was received from 3 physician specialty societies and 1 academic medical center while this policy was under review in 2010. In addition, unsolicited input was received from 1 foundation and 3 physicians. There was strong support for use of repository corticotropin in treatment of infantile spasms (West syndrome).

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

**American Academy of Neurology and Child Neurology Society**

In 2012, the American Academy of Neurology and the Child Neurology Society updated their evidence-based guidelines on the treatment of infantile spasms. The guidelines included the following recommendations on the use of adrenocorticotropic hormone (ACTH):
- “ACTH (Level B) or VGB [vigabatrin] (Level C) may be offered for short-term treatment of infantile spasms.”
- “Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms....”

**American College of Rheumatology**
In 2012, the American College of Rheumatology published guidelines on therapy and anti-inflammatory prophylaxis of acute gouty arthritis. The guidelines committee did not reach a consensus on use of ACTH for patients with acute gout who are able to take medications orally. For patients unable to take oral medications, the committee agreed that subcutaneous synthetic ACTH was a reasonable alternative to oral prednisone or prednisolone therapy.

**Infantile Spasms Working Group**
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 [electroencephalogram] in a randomized clinical trial setting (Mackay et al., 2004) and thus remain first-line treatment.”

**Gesellschaft für Neuropädiatrie**
A 2016 report, coordinated by the Gesellschaft für Neuropädiatrie (Society for Neuropediatrics), made the following relevant clinical recommendations:

- “ACTH is probably effective for the treatment of cryptogenic and symptomatic IS [infantile spasms].”
- “There are no data indicating superiority of any specific ACTH formulation (natural, synthetic, synthetic depot).”

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**
Not applicable.

**MEDICARE NATIONAL COVERAGE**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**
Some currently unpublished trials that might influence this review are listed in Table 2.

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02290444</td>
<td>Effects of Adrenocorticotropic Hormone (ACTHAR Gel) on Recovery From Cognitive Relapses in Multiple Sclerosis</td>
<td>60</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02132195a</td>
<td>Adrenocorticotropic Hormone (ACTH) for Frequently Relapsing and Steroid Dependent Nephrotic Syndrome</td>
<td>60</td>
<td>Oct 2018</td>
</tr>
<tr>
<td>NCT02315872a</td>
<td>The Effect of ACTH (Acthar) on Measures of Chronic Fatigue in Patients With Relapsing Multiple Sclerosis</td>
<td>90</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT01950234a</td>
<td>ACTH in Progressive Forms of MS</td>
<td>100</td>
<td>Dec 2020</td>
</tr>
</tbody>
</table>
### Unpublished

| NCT01601236<sup>a</sup> | A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Adaptive Design Pilot Safety and Efficacy Study of H.P. Acthar Gel (Acthar) in Patients With Diabetic Nephropathy and Proteinuria | 40 | Mar 2016 (completed) |
| NCT01386554<sup>a</sup> | Acthar for Treatment of Proteinuria in Membranous Nephropathy Patients (CHART) | 60 | May 2017 (completed) |

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

### REFERENCES


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>96372</td>
<td>Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J0800</td>
<td>Injection, corticotropin, up to 40 units</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>G40.821-G40.824</td>
<td>Epileptic spasms code range (includes infantile spasms)</td>
</tr>
<tr>
<td>ICD-10-PCS</td>
<td>3E013VJ</td>
<td>ICD-10-PCS codes are only used for inpatient services. There is no specific code for this procedure</td>
</tr>
</tbody>
</table>

**Type of Service**

**Place of Service**

**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/11/14</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 10, 2014. No change to policy statement. Reference 3 added.</td>
</tr>
<tr>
<td>12/10/15</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 13, 2015; reference 12 added. Not medically necessary due to costs statement for diagnostic testing and treatment of non-steroid-responsive conditions changed to investigational.</td>
</tr>
<tr>
<td>10/13/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 18, 2016; references 3 and 15 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>10/30/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes to policy as noted. Policy updated with literature review through August 28, 2017; no references added. Policy statements unchanged.</td>
</tr>
</tbody>
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