Introduction

Corticotropin is a hormone made in certain cells in the pituitary gland. (Corticotropin may also be known as ACTH or adrenocorticotropic hormone.) When corticotropin is produced in a lab and used as a treatment, it’s believed that it helps the body create its own natural steroid hormones. Corticotropin injections may be approved to treat a rare seizure disorder that affects infants, known as West syndrome. Corticotropin injections have also been tried for several other conditions known to respond to steroid treatments. When medical studies compared corticotropin treatment with intravenous steroids, the studies did not show that the corticotropin treatments worked better. For this reason, corticotropin treatment is considered not medically necessary for conditions where steroids are a proven treatment. Corticotropin has also been tried for many other conditions including gout and childhood epilepsy. There isn’t enough high quality medical evidence to show whether it works. For this reason, corticotropin treatment is considered investigational (unproven) for many conditions.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
### Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Repository corticotropin injection</strong>*</td>
<td><strong>Repository corticotropin injection may be considered medically necessary for treatment of infantile spasms (West syndrome).</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Repository corticotropin injection may be considered not medically necessary in the following corticosteroid-responsive conditions, including, but not limited to:</strong></td>
</tr>
<tr>
<td></td>
<td>- Multiple sclerosis, acute exacerbation in adults</td>
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<tr>
<td></td>
<td>- Rheumatic disorders such as: psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis</td>
</tr>
<tr>
<td></td>
<td>- Dermatologic diseases such as erythema multiforme, Stevens-Johnson syndrome</td>
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<td></td>
<td>- Nephrotic syndrome – idiopathic or due to systemic lupus erythematosus (SLE)</td>
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<td></td>
<td>- Ophthalmic diseases such as allergic and inflammatory processes of the eye: optic neuritis, keratitis, iritis, uveitis, choroiditis, chorioretinitis, anterior segment inflammation</td>
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<td></td>
<td>- Respiratory diseases such as symptomatic sarcoidosis</td>
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<td></td>
<td>- Allergic states such as serum sickness</td>
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<tr>
<td></td>
<td>- Collagen diseases such as systemic lupus erythematosus (SLE), systemic dermatomyositis (polymyositis)</td>
</tr>
</tbody>
</table>

**Repository corticotropin injection is considered not medically necessary for use in diagnostic testing of adrenocortical function.**

**Repository corticotropin injection is considered investigational for all other indications.**

*Note: The brand name for repository corticotropin is H.P. Acthar Gel®*
Repository corticotropin injection is considered investigational for conditions that are not responsive to corticosteroid therapy including, but not limited to:

- Acute gout
- Childhood epilepsy
- Use in tobacco cessation

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td>Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
</tr>
<tr>
<td>96372</td>
<td></td>
</tr>
<tr>
<td>HCPCS</td>
<td>Injection, corticotropin, up to 40 units</td>
</tr>
<tr>
<td>J0800</td>
<td></td>
</tr>
</tbody>
</table>

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### Related Information

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

### Consideration of Age

Any ages listed in the policy statements are based on FDA labeling.
Description

Repository corticotropin injection (H.P. Acthar® gel, Questcor Pharmaceuticals, Union City, CA) 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.

Background

H.P. Acthar® gel was approved by the FDA in 1952, before there was a requirement that companies provide clinical evidence of efficacy. In the intervening years numerous high quality corticosteroids (such as hydrocortisone, prednisone and methylprednisolone) became available and evolved as the standard of care in treating steroid sensitive conditions. These drugs are available at a much lower cost.

Repository corticotropin injection is best known and has supportive clinical data 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 (Sabril®) oral solution is another available treatment for infantile spasms.

Use of this agent in the management of multiple sclerosis exacerbations is considered not medically necessary because there is no evidence to support H.P. Acthar’s superiority to the standard of care treatment involving high quality corticosteroids (such as hydrocortisone, prednisone, and methylprednisolone).

Diagnostic testing of adrenocortical function, known as the ACTH test, is typically done with synthetic ACTH. Synthetic ACTH products have been approved by the FDA for this purpose.

Repository corticotropin injection has potential adverse effects similar to those that occur with steroid medication 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.
Summary of Evidence

**Infantile Spasms**

There is some evidence from small, generally poor quality RCTs, that natural and synthetic ACTH has greater short-term efficacy in resolving infantile spasms than vigabatrin. A 2014 RCT suggests that prednisolone may be at least as effective in the short term as synthetic ACTH in the treatment of infantile spasms.

**Corticosteroid-Responsive Conditions**

There is insufficient evidence that ACTH gel is at least as effective as IV corticosteroids for treatment of multiple sclerosis. One of 2 RCTs found that corticosteroids were more effective and the other found no significant difference in efficacy. There is a lack of evidence from controlled trials that ACTH is an effective treatment of other corticosteroid-responsive conditions. 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.

**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.11 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 H.P. Acthar gel for this purpose. 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.
Non-Corticosteroid-Responsive Conditions

There is insufficient evidence from controlled trials that ACTH is a safe and effective treatment of non-corticosteroid-responsive treatments.

Other

A study done by Lal et al looked at the pharmacodynamics and tolerability of repository corticotropin injection (ACTH) compared to IV methylprednisolone (IVMP).\textsuperscript{13} This was a multiple-dose, randomized, open-label crossover study that enrolled 18 healthy subjects to evaluate the total cortisol-equivalent exposure, effects on circulating immune cells, and tolerability of the study drug used. The authors concluded that ACTH may cause less systemic immunosuppression relative to equivalent doses of IVMP, which may be of benefit in autoimmune disorders, such as MS. This is a small study done in healthy subjects, which offered no clinical outcomes. Further studies are needed to substantiate these findings.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. 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>NCT01753401\textsuperscript{a}</td>
<td>A Two-part Study Exploring the Efficacy, Safety, and Pharmacodynamics of Acthar in Systemic Lupus Erythematosus Patients With a History of Persistently Active Disease</td>
<td>36</td>
<td>June 2017 (ongoing but not recruiting)</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>NCT02132195\textsuperscript{a}</td>
<td>Adrenocorticotropic Hormone (ACTH) for Frequently Relapsing and Steroid Dependent Nephrotic Syndrome</td>
<td>60</td>
<td>Oct 2018</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>NCT02315872</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>NCT01950234</td>
<td>Treatment of Progressive Forms of Multiple Sclerosis With Pulsed ACTH (Acthar Gel)</td>
<td>100</td>
<td>Dec 2020</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01601236</td>
<td>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</td>
<td>40</td>
<td>Mar 2016 (completed)</td>
</tr>
<tr>
<td>NCT01386554</td>
<td>A Randomized, Placebo-Controlled, Parallel-Group, Double-Blind Study of H.P. Acthar Gel (Acthar) in Treatment-Resistant Subjects With Persistent Proteinuria and Nephrotic Syndrome Due to Idiopathic Membranous Nephropathy (iMN)</td>
<td>60</td>
<td>May 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial

* Denotes industry-sponsored or cosponsored trial

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**Practice Guidelines and Position Statements**

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

In 2012, the American Academy of Neurology and the Practice Committee of the Child Neurology Society published an updated evidence-based guideline on treatment of infantile spasms.\(^\text{14}\) The guideline included the following recommendations regarding use of ACTH:

- ACTH or vigabatrin may be useful for the short-term treatment of infantile spasms
- ACTH should be preferred over vigabatrin
- Hormonal therapy (ACTH or prednisolone) may be considered for treatment of infants with cryptogenic infantile spasms
Infantile Spasms Working Group

In 2010, an industry-sponsored Infantile Spasms Working Group published a consensus report on diagnosis and treatment of infantile spasms.\textsuperscript{16} 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.”

References


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/09/16</td>
<td>New policy. Policy created to include plan specific medically necessary indications; replaces policy 5.01.17. Repository corticotropin injection may be considered medically necessary when criteria are met.</td>
</tr>
<tr>
<td>06/01/16</td>
<td>Interim Update, approved May 10, 2016. Language clarified regarding use the drug for steroid responsive conditions. FDA labeled conditions approved in 1952 were prior to the commercial availability of corticosteroid agents and not based on studies showing efficacy. Corticosteroid agents are available at lower cost and have stronger scientific evidence regarding their efficacy for most conditions, thus making this product not medically necessary based on contract language.</td>
</tr>
<tr>
<td>12/01/17</td>
<td>Annual Review, approved November 9, 2017. Policy updated with literature review through August 2017; no references added. Policy statements for corticosteroid-responsive conditions reorganized for clarity, including adding ophthalmic diseases.</td>
</tr>
<tr>
<td>09/21/18</td>
<td>Minor update. Added Consideration of Age statement.</td>
</tr>
</tbody>
</table>

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

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Email AppealsDepartmentInquiries@Premera.com

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