Policy

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

Repository corticotropin injection may be considered not medically necessary in the following conditions:

- Multiple sclerosis, acute exacerbation in adults
- Rheumatic disorders such as: psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis
- Inflammatory dermatology conditions such as erythema multiforme, Stevens-Johnson’s syndrome, polymyositis, systemic dermatomyositis
- Nephrotic syndrome – idiopathic or due to systemic lupus erythematosus (SLE)
- Sarcoidosis
- Serum sickness
- Systemic lupus erythematosus (SLE)

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.

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

*The brand name for repository corticotropin is H.P. Acthar Gel®

Related Policies

None
Policy Guidelines

Coding

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

Description

Background

Pharmacology

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.

H.P. Acthar® gel was approved by 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 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.

Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Benefit Application

N/A

Rationale

This policy was created in January, 2016 with searches of the MEDLINE database. Following is a summary of the key literature.

Evidence that Acthar Gel (i.e., 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, i.e., fewer than half the study reported the method of randomization, and only 2 studies 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, an 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 FDA-approved 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 range, score of 0-16). Hypsarrhythmia is an abnormal interictal pattern seen on an electroencephalogram (EEG) 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 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.

Section Summary: 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
The product label for H.P. Acthar gel (i.e. 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. There is minimal scientific evidence for most of these conditions.

Multiple Sclerosis
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.

Sismarian and colleagues (2011) reported on a small prospective, randomized, open-label pilot trial of a 5-day self-administered ACTH dosing protocol for multiple sclerosis exacerbations. The routes of medication administration, intramuscular and subcutaneous, were compared. (9) There were 20 participants enrolled (mean age 39.5 years) with 19 completing the trial. Results were evaluated on day 7 and day 14 using 5 assessment tools that included physical and psychological responses. On day 14, 61.1% of patients (11 of 18 with day 14 scores) were treatment responders, and rated their condition as “very much improved” or “much improved”. The authors concluded that a 5-day course of "patient-administered" ACTH gel therapy as a potential substitute for the standard 14-day treatment may improve acute exacerbations of multiple sclerosis symptoms using either intramuscular or subcutaneous injections. Larger, placebo-controlled studies are needed to determine the optimal dose of ACTH gel, duration of treatment, and route of administration, as well as its role compared with steroid therapy.

Other corticosteroid-responsive conditions
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 nephritic 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. (10) 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 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 7 of 21 (33%) patients had a partial remission (at least a 50% reduction in proteinuria and final proteinuria 500-3500 mg/day).

Section Summary: 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.

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 Acthar gel for this purpose.

Non-Corticosteroid-Responsive Conditions
Repository corticotropin injection has also been proposed for several off-label non-steroid-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 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. (12) Three head-to-head trials were identified; 1 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.”

Section Summary: 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). (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

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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT01753401a</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>Dec 2015</td>
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<tr>
<td>NCT01601236a</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>Jan 2016</td>
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<tr>
<td>NCT02290444</td>
<td>Effects of Adrenocorticotropic Hormone (ACTHAR Gel) on Recovery From Cognitive Relapses in Multiple Sclerosis</td>
<td>60</td>
<td>Aug 2016</td>
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<tr>
<td>NCT01386554a</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>
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<td>NCT02132195a</td>
<td>Adrenocorticotropic Hormone (ACTH) for Frequently Relapsing and Steroid Dependent Nephrotic Syndrome</td>
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<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 2017</td>
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<tr>
<td>NCT01950234a</td>
<td>Treatment of Progressive Forms of Multiple Sclerosis With</td>
<td>100</td>
<td>Dec 2018</td>
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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. (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. (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 hyparrhythmic EEG in a randomized clinical trial setting (Mackay et al., 2004) and thus remain first-line treatment."

### References


Appendix

N/A

History

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<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>
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<tr>
<td>05/10/16</td>
<td>Interim Update. 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>
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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). ©2016 Premera All Rights Reserved.
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  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
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  - Qualified interpreters
  - Information written in other languages

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Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalina nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyon yon watchdog apan Premera Blue Cross. Daytoy ket mabalina dagiti importante a pelsa iti daytoy a pakdaar. Mabalina nga adda rumbang nga aramidenyo nga addang sakbay dagiti partikular a nalitung nga alaw napot mapagalatnedyo a tiyage ti salan-ayno yon watchdog kadtig stigos. Adda karbenganyo a mangala iti daytoy nga impormasion ken watchdog iti bukodayo a pagasasao nga awan ti bayadanoy. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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