REPOSITORY CORTICOTROPIN INJECTION (H.P. ACTHAR GEL®)

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INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines®, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

Repository corticotropin injection (H.P. Acthar Gel) is proven for the treatment of:

1. Infantile spasm (i.e., West Syndrome) for up to 4 weeks when all of the following criteria are met:
   A. Diagnosis of infantile spasms (i.e., West Syndrome)
   -AND-
   B. Patient is less than 2 years old
   -AND-
   C. Repository corticotropin injection dosing for infantile spasm is as follows:
      a. Initial dose: 75 U/m² intramuscular (IM) twice daily for 2 weeks.
      b. After 2 weeks, dose should be tapered according to the following schedule:
         30 U/m² IM in the morning for 3 days; 15 U/m² IM in the morning for 3 days;
10 U/m² IM in the morning for 3 days; and 10 U/m² IM every other morning for 6 days (3 doses).

Additional information to support medical necessity review where applicable:
The above indication and criteria also apply to medical necessity review.

2. Opsoclonus-myoclonus syndrome (i.e., OMS, Kinsbourne Syndrome)¹

3. Multiple sclerosis (MS), acute exacerbation¹

Additional information to support medical necessity review where applicable:
Repository corticotropin injection is not medically necessary for treatment of acute exacerbations of multiple sclerosis. Published clinical evidence does not demonstrate superiority of Acthar to other available corticosteroids.

Repository corticotropin injection is unproven and not medically necessary for treatment of the following:

1. Rheumatic Disorders: psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis, anklyosing spondylitis
2. Collagen Diseases: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)
3. Dermatologic Diseases: Severe erythema multiforme, Stevens-Johnson syndrome
4. Allergic States: Serum sickness
5. 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
6. Respiratory Diseases: Symptomatic sarcoidosis
7. 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.
8. Any indication outside of the proven indications above

Repository corticotropin injection has additional suggested uses listed in the FDA-label¹; however, these are not explicit labeled indications, and in the absence of statistically robust randomized controlled trials, there is insufficient evidence to establish the safety and efficacy of repository corticotropin injection for these conditions.

Centers for Medicare and Medicaid Services (CMS):
Medicare does not have a National Coverage Determination (NCD) for H.P. Acthar (repository corticotropin injection). Local Coverage Determinations do exist. Refer to the LCDs for Corticotropin.

In general, Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, Section 50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf

(Accessed February 11, 2014)

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances. Where such mandates apply, they supersede language in the benefit document.
or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

**The State of New Jersey prohibits requiring failed prior therapy or intolerance to therapy as a requirement for coverage.

**BACKGROUND**

Repository corticotropin injection (H.P. Acthar Gel) is an adrenocorticotropic hormone (ACTH) analogue.1-3 Repository corticotropin injection and ACTH stimulate the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. Prolonged administration of large doses of repository corticotropin injection induces hyperplasia and hypertrophy of the adrenal cortex and continuous high output of cortisol, corticosterone and weak androgens. The release of endogenous ACTH is influenced by the nervous system via the regulatory hormone released from the hypothalamus and by a negative corticosteroid feedback mechanism. Elevated plasma cortisol suppresses ACTH release. Repository corticotropin injection also binds to melanocortin receptor. Both endogenous ACTH and repository corticotropin injection have a trophic effect on the adrenal cortex which is mediated by cyclic adenosine monophosphate (cyclic AMP).

**CLINICAL EVIDENCE**

**Proven Uses**

**Infantile Spasms (i.e., West Syndrome)**

Approval of ACTH for the treatment of infantile spasms (IS) was based on one pivotal and one supportive clinical trial. Unlike the conventional process for drug approvals, in which pivotal studies are submitted to the FDA for approval, Questcor Pharmaceuticals re-analyzed data from the previously published studies; there was no prospectively defined statistical analysis. In both clinical trials, patients were evaluated by electroencephalogram (EEG) before initiation of treatment (to confirm the presence of clinical spasms and the EEG pattern) and after the end of the treatment period to evaluate response to therapy. The primary outcome, overall response, defined as complete cessation of spasms and resolution of the EEG pattern on video EEG, is a widely accepted definition of clinical success in the expert community. Baram and colleagues published a pivotal, single-blind study comparing high-dose ACTH administered as 75 Units/m² IM BID (150 mg Units QD) and prednisone 2 mg/kg/day given as 1 mg/kg PO BID.4 Infants with clinical IS and no previous steroid or ACTH treatment were randomized to receive ACTH (n = 15) or prednisone (n = 14) for 2 weeks with a gradual taper to zero for an additional 2 weeks. Patients with persistent spasms or hypsarrhythmia after initial treatment were offered the alternative treatment. The Questcor analysis of the efficacy data demonstrated that the combined clinical endpoint of spasm cessation and resolution of hypsarrhythmic EEG favored ACTH (13/15, 86.7%) compared to prednisone (4/14, 28.6%) (p < 0.002). The difference between ACTH and prednisone was significant for both EEG response (86.7% vs. 28.6%, p = 0.0015) and spasm cessation (93.3% vs. 28.6%, p = 0.0003). For patients who did not respond to the original treatment and were crossed-over to alternative therapy, results showed that 1 of 2 patients who failed ACTH responded to prednisone and 7 of 8 patients (87.5%) who did not respond to prednisone responded to ACTH.5 Even though this pivotal study showed that ACTH was superior to prednisone in IS, the lack of pre-specified statistical analysis and the limited power to detect a difference in response rates in the re-analysis are limitations.

The supportive efficacy study was a prospective, randomized, controlled, single-blind trial.6 Patients were randomized to treatment with once-a-day low-dose (LD) ACTH (20 Units IM QD, n = 29) for a short-duration (2 weeks treatment followed by a 2 weeks taper in responders or a dose escalation to 30 Units/d in non-responders) or once-a-day high-dose (HD) ACTH (150 Units/m² QD n = 30) for a long-duration (3 weeks treatment followed by a 9 week taper). Even
though 59 patients were enrolled in the study, 9 of them did not complete the treatment protocol, which had a considerable impact on the results of the study. Information was recovered for 8 of these patients. In the intent-to-treat (ITT) population, which included all 59 randomized patients, there was no significant difference between the HD and LD groups in overall response (50% vs. 52%, p = 0.94) or either of the 2 secondary endpoints: spasm control alone (77% vs. 55%, p = 0.07) or EEG response alone (53% vs. 62%, p = 0.52). An independent analysis by the sponsor was based on a modified intent-to-treat (mITT) population (n = 51), which included all patients who received at least one dose of drug and had adequate data for evaluation. The overall response rate (62.5% vs. 48.1%, p = 0.2768) was also non-significant, which was attributed to the once-daily administration of ACTH in this trial. Analysis of the secondary efficacy results in the mITT population did not establish significance for the hypsarrhythmic EEG pattern response rate, but demonstrated a greater spasm control response rate in the HD group (79.2%, 19/24) than in the LD group (51.9%, 14/27) with nominal statistical significance (p = 0.0329).

Kivity et al. evaluated the long-term cognitive and seizure outcomes of a cohort of 37 patients with cryptogenic infantile spasms, with onset age 3–9 months, receiving a standardized treatment regimen of high dose tetracosactide depot, 1 mg IM every 48 h for 2 weeks, with a subsequent eight- to ten-week slow taper and followed by oral prednisone, 10 mg/day for a month, with a subsequent slow taper for five months or until the infant reached the age of one year, whichever came later. Seizure outcomes were followed up prospectively. Cognitive outcomes were determined after 6–21 years and analyzed in relation to treatment lag and pretreatment regression. A total of 22 infants were treated within one month of onset of infantile spasms, and 15 after one to 6.5 months. Normal cognitive outcome was found in all 22 (100%) patients of the early-treatment group, and in 40% of the late-treatment group. Normal cognitive outcome was found in all 25 (100%) patients who had no or only mild mental deterioration at presentation, including four in the late-treatment group but in only three of the 12 patients who had had marked or severe deterioration before treatment. Results showed that early treatment of cryptogenic infantile spasms with a high-dose ACTH protocol is associated with favorable long-term cognitive outcomes. However, the author concluded that further studies are needed on the optimal treatment regimen for this disorder.

Opsoclonus-Myoclonus Syndrome (i.e., OMS, Kinsbourne Syndrome)
Cerebrospinal fluid (CSF) adrenocorticotropic hormone (ACTH) concentration and cortisol were measured in 69 children with opsoclonus-myoclonus syndrome (OMS) and 25 age- and sex matched control subjects to determine endogenous levels and to look for hypothesized differential hormonal effects of ACTH and corticosteroid treatment. To compare high-dose versus low-dose, the ACTH-treated group was divided at the median (32 IU/m2/day) and the steroid group was also divided at the median (1.5 mg/kg/day). In cases of alternate day dosing, the dose was halved as an approximation for comparison with the daily dose group. CSF cortisol was 10-fold higher in the 26 patients receiving ACTH treatment (p<0.05), but was unchanged with oral steroid treatment (n = 18) or no treatment (n = 25). It was significantly higher (25-fold) in children receiving daily high-dose ACTH than alternate day ACTH. In ACTH-treated children, CSF and serum cortisol were highly correlated (r=0.0001), with a mean ratio of CSF to serum cortisol of approximately 1:10. CSF ACTH concentration did not differ significantly between untreated OMS and control subjects but was lower with ACTH (-29%) or steroid treatment (-36%), suggesting feedback inhibition of ACTH release (p<0.05). Results indicated that daily high-dose ACTH treatment dramatically raises the concentration of CSF cortisol, but alternate day and low-dose ACTH did not. Researchers conclude that to the extent that cortisol is a factor in clinical response to ACTH therapy, data supports the use of high-dose ACTH protocols in OMS. Additionally, elevated brain cortisol may contribute to the superiority of ACTH treatment over oral corticosteroids in inducing a neurologic remission in OMS.

Pranzatelli et al. evaluated the effects of adrenocorticotropic hormone (ACTH) treatment on the clinical findings and CSF levels of levels of cerebrospinal fluid (CSF) Dopa, catecholamines, deaminated metabolites of catecholamines, as well as homovanillic acid (HVA) and 5-
hydroxyindoleacetic acid (5-HIAA) in 8 children (age range 1.6 – 4.4 years) diagnosed with opsinclonus-myoclonus.\textsuperscript{1,17} Patients were evaluated prior to ACTH treatment and after 2 months on treatment. In addition to CSF level measurements (via lumbar punctures), patients were graded on opsinclonus, myoclonus, ataxia, irritability and functional disability (0=absent, 1=mild, 2=moderate, and 3=severe). Researchers used a modified ACTH regimen of a high-dose schedule for infantile spasms, starting with 75 IU/m2 administered intramuscularly twice a day for 1 week, then daily for 1 week, every other day for 2 weeks, then tapered over 16 weeks (70, 60, 50, 45, 35, 25, 15, 10, 8 IU/m2) on alternating days, remaining at the lowest dose for 4 weeks. At the time of the second lumbar puncture, the patients were receiving approximately 60 IU/m2 (range, 45-75 IU/m2) on alternate days. All patients responded to ACTH treatment. Outcomes showed that ACTH treatment significantly reduced neurologic abnormality in children with OMS (p=0.001) with mean improvement in severity scores reported as 70% for opsinclonus, 52% for myoclonus, 50% for ataxia, 55% for irritability, and 57% for overall functional disability. Treatment with ACTH reduced the HVA concentration in every child by a mean of 21% (p < 0.001). ACTH therapy was associated with significant correlations between dopaminergic markers such as HVA, dihydroxyphenylacetic acid (DOPAC), and Dopa. There were no significant changes in the CSF concentrations of the noradrenergic markers norepinephrine (NE) and dihydroxyphenylglycol (DHPG), or in the serotonergic marker 5-HIAA. Researchers conclude that the beneficial effects of ACTH in OMS are not associated with normalization of HVA or 5-HIAA levels. Additionally, the pattern of decreased HVA and unchanged DOPAC levels could reflect decreased extraneuronal uptake of catecholamines (which steroids inhibit) or decreased O-methylation of catecholamines in nonneuronal cells.

\textbf{Unproven}

H.P. Acthar has additional uses listed in the FDA-label:\textsuperscript{1}

- Rheumatic Disorders: psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis, ankylosing spondylitis
- Collagen Diseases: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)
- Dermatologic Diseases: Severe erythema multiforme, Stevens-Johnson syndrome
- Allergic States: Serum sickness
- 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
- Respiratory Diseases: Symptomatic sarcoidosis
- 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.

Statistically robust randomized controlled trials are necessary to establish the safety and efficacy of H.P. Acthar to treat these conditions.\textsuperscript{1,8-12,18-20}

\textbf{Technology Assessments}

In 2013, an update to the 2000 Cochrane review was published evaluating efficacy and safety of corticosteroids or adrenocorticotropic hormone (ACTH) in reducing short and long term morbidity associated with multiple sclerosis (MS).\textsuperscript{14} Authors concluded that:

- The trials evaluated showed that corticosteroids (methylprednisolone (MP)) or ACTH favored recovery from acute exacerbation in MS, which increased the probability of ameliorating the episode within the first five weeks of treatment by more than 60%. Evidence found that corticosteroids, notably MP, are effective in the treatment of acute exacerbation, increasing the probability of ameliorating the episode and speeding up patient recovery.
• There was insufficient evidence to determine if steroids or ACTH treatment prevented new exacerbations and worsening of long term disability in MS.
• Evidence on the efficacy of different types or schedules of therapies was limited. Indirect comparisons suggest a significantly greater effect of MP versus ACTH.

In 2010, the Infantile Spasms Working Group (ISWG) developed a consensus of the U.S. approach to the diagnostic evaluation and treatment of infantile spasms.\textsuperscript{15} There was strong consensus on the following four conclusions:

• The need for broad clinical evaluation, including detailed clinical neurophysiology was strongly recommended.
• ACTH and vigabatrin are the only drugs with proven effectiveness to suppress clinical spasms and abolish the hypsarrhythmic EEG (a specific EEG pattern found only in this syndrome) in a randomized clinical trial setting and thus remain first line treatments.
• Regardless of the chosen medication, timely assessment of treatment efficacy, i.e., two weeks for ACTH followed by taper (two weeks or less following dose titration for vigabatrin) and, if indicated, prompt treatment modification is strongly recommended as longer treatment trials, i.e. greater than two weeks for ACTH; greater than three months for vigabatrin are not likely to be effective and may come at the expense of serious adverse events.
• Effective treatment for infantile spasms should produce both cessation of spasms and resolution of hypsarrhythmia on EEG and is an all or none “response.”

**Professional Societies**

In 2012, the American Academy of Neurology (AAN) updated their 2004 evidence-based guideline which summarizes the most effective therapies for infantile spasms, their safety, and whether successful treatment of infantile spasms leads to long-term improvement.\textsuperscript{13,21} The recommendations of the AAN and Child Neurology Society (CNS) regarding medical treatment of infantile spasms in children is as follows for adrenocorticotropic hormone (ACTH):

A. The evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as ACTH for short-term treatment of infantile spasms (Level U).
B. Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B).
C. ACTH (Level B) or VGB (Level C) may be offered for short-term treatment of infantile spasms. Evidence suggests that ACTH may be offered over VGB (Level C).
D. Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome (Level C).
E. A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB may be considered to improve long-term cognitive outcomes (Level C).

**AAN Rating of Recommendation:**

• Level A: Established as effective, ineffective or harmful for the given condition in the specified population
• Level B: Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population.
• Level C: Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population.
• Level U: Data inadequate or conflicting. Given current knowledge, treatment is unproven.
H.P. Acthar Gel is an adrenocorticotropic hormone (ACTH) analogue indicated as monotherapy for the treatment of infantile spasms in infants and children less than 2 years of age and for the treatment of exacerbations of multiple sclerosis in adults. H.P. Acthar Gel may be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous states.¹

### APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document.

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<th>HCPCS Code</th>
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<td>J0800</td>
<td>Injection, corticotropin, up to 40 units</td>
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<tr>
<th>ICD-9 Code</th>
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<tr>
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<td>Myoclonus</td>
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<tr>
<td>333.90</td>
<td>Unspecified extrapyramidal disease and abnormal movement disorder</td>
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<td>340</td>
<td>Multiple sclerosis (only for those members without medical necessity)</td>
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<td>345.60</td>
<td>Infantile spasms without mention of intractable epilepsy</td>
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<td>345.61</td>
<td>Infantile spasms with intractable epilepsy</td>
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<td>379.59</td>
<td>Other irregularities of eye movements (Opsoclonus)</td>
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ICD-10 Codes (Preview Draft)

In preparation for the transition from ICD-9 to ICD-10 medical coding on October 1, 2015*, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.

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<td>G25.9</td>
<td>Extrapyramidal and movement disorder, unspecified</td>
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<td>G35</td>
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<td>H55.89</td>
<td>Other irregular eye movements</td>
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### REFERENCES


H.P. Acthar: Drug Policy (Effective 08/01/2014)
### POLICY HISTORY/REVISION INFORMATION

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<td>medically necessary criteria, CMS, Clinical Evidence and References. Approved by National Pharmacy &amp; Therapeutics Committee on 5/21/2014. Policy</td>
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