

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

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[Instructions for Use](#) ⓘ

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## Related Policies

None

## COVERAGE RATIONALE

See [Benefit Considerations](#) ⓘ

### H.P. Acthar Gel (repository corticotropin injection) is proven and medically necessary for the treatment of:

- I. **Infantile spasm** (i.e., West Syndrome)<sup>1</sup> 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. Physician attestation that there is no competent caregiver to administer the drug. Physician must submit explanation; **and**
  - D. H.P. Acthar Gel dosing for infantile spasm is as follows:
    1. Initial dose: 75 U/m<sup>2</sup> intramuscular (IM) twice daily for 2 weeks.
    2. After 2 weeks, dose should be tapered according to the following schedule: 30 U/m<sup>2</sup> IM in the morning for 3 days; 15 U/m<sup>2</sup> IM in the morning for 3 days; 10 U/m<sup>2</sup> IM in the morning for 3 days; and 10 U/m<sup>2</sup> IM every other morning for 6 days (3 doses).
- II. **Opsoclonus-myoclonus syndrome** (i.e., OMS, Kinsbourne Syndrome) when **both** of the following criteria are met:
  - A. Diagnosis of Opsoclonus-myoclonus syndrome (i.e., OMS, Kinsbourne Syndrome); **and**
  - B. Physician attestation that there is no competent caregiver to administer the drug. Physician must submit explanation.

### H.P. Acthar Gel is not medically necessary for treatment of acute exacerbations of multiple sclerosis.

For non-medical necessity plans, H.P. Acthar Gel may be covered for the treatment of acute exacerbation of multiple sclerosis (MS).

Although FDA labeling suggests that H.P. Acthar may be used in the following conditions, it is not FDA indicated.

### H.P. Acthar Gel is unproven and not medically necessary for treatment of the following disorders and diseases:

- 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
- Any indication outside of the proven indications above

## U.S. FOOD AND DRUG ADMINISTRATION (FDA)

H.P. Acthar Gel is an adrenocorticotrophic 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. The FDA labeling suggests that H.P. Acthar Gel may be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous states, however, it is not FDA indicated for these conditions.<sup>1</sup>

## BACKGROUND

H.P. Acthar Gel is an adrenocorticotrophic hormone (ACTH) analogue.<sup>1-3</sup> 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).

## APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
J0800	Injection, corticotropin, up to 40 units
ICD-10 Diagnosis Code	Description
G25.3	Myoclonus
G25.9	Extrapyramidal and movement disorder, unspecified
G35	Multiple sclerosis ( <i>only for those members without medical necessity</i> )
G40.821	Epileptic spasms, not intractable, with status epilepticus
G40.822	Epileptic spasms, not intractable, without status epilepticus
G40.823	Epileptic spasms, intractable, with status epilepticus
G40.824	Epileptic spasms, intractable, without status epilepticus
H55.89	Other irregular eye movements

## BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for 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 when certain conditions are met. 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.

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

In a single-center, single-blind, parallel-group, randomized clinical trial, Wanigasinghe et al, investigated whether ACTH is not superior to high-dose prednisolone for treatment of newly diagnosed West Syndrome (WS).<sup>23</sup> Ninety-seven infants, newly diagnosed with WS, were randomized to receive either 14 days of oral prednisolone (40 to 60 mg/day) or an intramuscular (IM) injection of ACTH (40 to 60 IU/ every other day). This followed the United Kingdom Infantile Spasm Study protocol. Infantile spasm (IS) remission was blindly evaluated by day 14, including using a 30 minute electroencephalograph (EEG) as well as continued spasm freedom for 28 days. Forty-eight infants received prednisolone and 49 infants received ACTH. By day 14, cessation of infantile spasms occurred in 58.3% of infants (28/48) on prednisolone, compared with only 36.7% (18/49) of infants given ACTH (P=0.03). EEG and spasm cessation showed electroclinical remission in 21 prednisolone infants versus 9 ACTH infants (P = 0.008). Days required for spasm remission was significantly less in the prednisolone group (3.85 days ± 2.4) compared with ACTH (8.65 days ± 3.7) (P = 0.001). The authors concluded that ACTH therapy at the trial dose did not yield superior rates of EEG or clinical remission when compared with the trial dose of prednisolone. More patients achieved electroclinical remission when treated with prednisolone than with ACTH.

**Opsoclonus-Myoclonus Syndrome (i.e., OMS, Kinsbourne Syndrome)**

Tate et al evaluated the efficacy and safety of corticotropin-based immunotherapies in a prospective, rater-blinded, exploratory study of previously untreated or steroid-dependent children (n=74) with opsoclonus-myoclonus syndrome (OMS).<sup>17</sup> Children with neuroblastomas were excluded. Children were put into 1 of 6 groups: corticotropin alone or with intravenous immunoglobulin (groups 1 and 2, active controls); or both with rituximab (group 3) or cyclophosphamide (group 4); or with rituximab plus chemotherapy (group 5) or steroid spacers (group 6). Data was obtained through the Corticotropin Intake Form and Opsoclonus-Myoclonus Evaluation Scale. The primary end points were reduction in clinical severity relative to baseline (posttreatment total score and percentage improvement in total score). Researchers found that there was a 65% improvement in motor severity score across groups (p<0.0001), but treatment combinations were more effective than corticotropin monotherapy (p=0.0009). Groups 3, 4, and 5 responded better than group 1; groups 3 and 5 responded better than group 2. The response frequency to corticotropin was higher than to prior corticosteroids (p<0.0001). Adverse events (corticosteroid excess) were reported in 55% of children, more so with multiagents (p=0.03); and 10% of children (n=7) had serious adverse events which were heterogeneous in etiology. Researchers concluded that the study demonstrated the greater efficacy of corticotropin-based multimodal therapy compared with conventional therapy and a greater response to corticotropin than corticosteroid-based therapy.

Cerebrospinal fluid (CSF) adrenocorticotrophic 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.<sup>16</sup> To compare high-dose versus low-dose, the ACTH-treated group was divided at the median (32 IU/m<sup>2</sup>/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 (p=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.

**Unproven**

H.P. Acthar Gel has additional uses listed in the FDA-label however, it is not FDA indicated. Since H.P. Acthar is more costly than an alternative drug that is at least as likely to produce equivalent therapeutic results, UHCP has determined that use of H.P. Acthar Gel is unproven and not medically necessary for treatment of the following disorders and diseases<sup>1,8-12,18-20</sup>

- 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.

### **Technology Assessments**

In October 2014, The National Institute for Health and Care Excellences (NICE) published an updated clinical guideline entitled Management of Multiple Sclerosis (MS) in Primary and Secondary Care (Clinical Guideline 186).<sup>22</sup> In this publication, the Guideline Development Group (GDG) noted that some evidence for steroid use comes from older trials that had used ACTH but that ACTH is no longer used as a treatment option for acute relapse of MS. The GDG considered that steroids are the common accepted treatment for relapse and that delivery is dependent on service organization.

In 2013, an update to the 2000 Cochrane review was published evaluating efficacy and safety of corticosteroids or adrenocorticotrophic hormone (ACTH) in reducing short and long term morbidity associated with multiple sclerosis (MS).<sup>14</sup> 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 2013, a Cochrane review was published comparing the effects of single drugs used to treat infantile spasms in terms of long-term psychomotor development, spasm control, subsequent epilepsy, and adverse effects.<sup>24</sup> Authors concluded that:

- To date, few well-designed randomized controlled trials have considered the treatment of infantile spasms, and the numbers of patients enrolled have been small.
- In the majority, methodology has been poor, hence it is not clear which treatment is optimal in the treatment of this epilepsy syndrome.
- Hormonal treatment resolves spasms in more infants than vigabatrin, but this may or may not translate into better long-term outcomes.
- If prednisolone or vigabatrin is used, high dosage is recommended.
- Vigabatrin may be the treatment of choice in tuberous sclerosis.
- Resolution of the EEG features may be important, but this has not been proven.
- Further research using large studies with robust methodology is required.

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.<sup>15</sup> 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 2015, a Task Force for the ILAE Commission of Pediatrics developed a consensus document addressing diagnostic markers, management interventions, and outcome measures for infants with seizures. For ACTH, the task force concluded that for epileptic spasms, both high and low dose ACTH therapy is probably effective and the task force strongly recommends.<sup>25</sup>

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.<sup>13,21</sup> The recommendations of the AAN and Child Neurology Society (CNS) regarding medical treatment of infantile spasms in children is as follows for adrenocorticotrophic hormone (ACTH):\*

- 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).
- Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B).
- 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).
- 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).
- 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.

## CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for H.P. Acthar<sup>®</sup> (repository corticotropin injection). Local Coverage Determinations (LCDs) do not exist at this time.

Medicare may cover 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. See the [Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals](#). (Accessed March 27, 2018)

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#### POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
03/01/2019	Reorganized policy template; simplified and relocated <i>Instructions for Use and Benefit Considerations</i> section. Archived previous policy version 2018D0037J.
06/01/2018	Annual review. No changes to coverage rationale. Updated U.S. FDA, CMS statement, clinical evidence, and references. Approved by National Pharmacy & Therapeutics Committee on 05/18/2018. Policy 2017D0037I archived.
09/01/2017	Annual review. Updated coverage rationale. Updated CMS statement, clinical evidence, and references. Approved by National Pharmacy & Therapeutics Committee on 06/28/2017. Policy 2017D0037H archived.
02/01/2017	Updated policy to clarify clinical intent. Approved by National Pharmacy & Therapeutics Committee on 12/21/2016. Policy 2016D0037G archived.
07/01/2016	Annual review with no changes to Coverage Rationale. Updated CMS statement, Clinical Evidence and References. Approved by National Pharmacy & Therapeutics Committee on 05/20/2016. Policy 2015D0037F archived.
10/01/2015	Updated Applicable Codes for ICD-10 transition. Policy 2015D0037E archived.
08/01/2015	Annual review with no changes to Coverage Rationale. Updated CMS, Benefits, Clinical Evidence and References. Approved by National Pharmacy & Therapeutics Committee on 05/20/2015. Policy 2014D0037D archived.
08/01/2014	Revised proven criteria to allow coverage for IS, OMS & MS only. Medical necessity criteria will allow coverage for IS & OMS. Updated unproven and not medically necessary criteria, CMS, Clinical Evidence and References. Approved by National Pharmacy & Therapeutics Committee on 05/21/2014. Policy 2013D0037C archived.
12/01/2013	Clarified indication for infantile spasm under Coverage Rationale. Approved by National Pharmacy & Therapeutics Committee on 08/20/2013. Policy 2013D0037B

Date	Action/Description
	archived
06/01/2013	Annual review of policy. Clinical evidence and references updated. Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/2014. Approved by National Pharmacy & Therapeutics Committee on 04/09/2013. Policy 2013D0037A archived.
04/01/2013	New policy 2013D0037A. Approved by National Pharmacy & Therapeutics Committee on 05/15/2012.

## INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Drug Policies 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.