**POLICY:** H.P. Acthar® Gel (repository corticotropin injection for intramuscular or subcutaneous use – Mallinckrodt)

**DATE REVIEWED:** 03/25/2020

## OVERVIEW

H.P. Acthar gel (Acthar) 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.[1] Acthar is also indicated for the treatment of exacerbations of multiple sclerosis (MS) in adults. Controlled clinical trials have demonstrated Acthar gel to be effective in speeding the resolution of acute exacerbations of MS. However, there is no evidence that Acthar impacts the ultimate outcome or the natural history of the disease. According to the prescribing information, Acthar may be used for the following disorders and diseases: rheumatic disorders as an adjunctive therapy for short-term administration to tide the patient over an acute episode or acute episode or exacerbation (in psoriatic arthritis, rheumatoid arthritis [including juvenile rheumatoid arthritis {selected cases may require low-dose maintenance therapy}, and ankylosing spondylitis); collagen diseases (during an exacerbation or as a maintenance therapy in selected cases of systemic lupus erythematosus [SLE] and systemic dermatomyositis [polymyositis]); dermatologic diseases (severe erythema multiforme, Stevens-Johnson syndrome); allergic states (serum sickness); ophthalmic diseases for 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); and edematous states (e.g., 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).[1] However, data from controlled studies demonstrating efficacy are limited.

## Guidelines

In 2012 the American Academy of Neurology (AAN) and the Child Neurology Society updated the evidence-based guideline for the medical treatment of infantile spasms.[2] The guidelines note that ACTH is a first-line agent for the short-term treatment of infantile spasms. The Infantile Spasms Working Group (ISWG) published a US consensus report on infantile spasms in 2010.[3] Data regarding ACTH use in infantile spasms were detailed and it was determined that ACTH is an effective first-line therapy for infantile spasms.[3] Published data are also available.[4-8] The incidence of infantile spasms ranges from 2 to 3.5 per 10,000 live births and most patients present between the ages of 3 months to 7 months; 90% of patients present in the first year of life. Onset after 18 months of age is rare, although onset up to 4 years of age has been reported.[2] Infantile spasms are a catastrophic form of epilepsy in children and poor developmental outcome may result. The recommended duration therapy for Acthar is short-term (2 weeks of treatment followed by a gradual taper and discontinuation over a 2-week period).

For the management of MS relapses, high-dose corticosteroids are the accepted standard of care short-term.[36] The most common regimen is 500 to 1,000 mg of intravenous methylprednisolone given daily for 3 to 5 days, with or without an oral steroid tapering regimen (most often prednisone) for 1 to 3 weeks.[36] Acthar and high-dose intravenous methylprednisolone have been shown to possess similar efficacy in the management of MS relapses.[37]

## POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Acthar. Because of the specialized skills required for evaluation and diagnosis of patients with these conditions, as well as monitoring required for adverse events and efficacy, approval requires Acthar to be prescribed by or in

consultation with a physician who specializes in the conditions being treated. All approvals are provided for 1 month in duration, where 1 month is equal to 30 days, unless otherwise noted below.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Acthar Gel is recommended in those who meet the following criteria:

### FDA-Approved Indications

1. **Infantile Spasms, Treatment.** Approve for 1 month if the patient meets both of the following criteria (A and B):
   **A)** The child is less than 2 years of age; AND
   **B)** Acthar is prescribed by or in consultation with a neurologist.

   **Dosing.** Approve up to 150 units/$m^2$ by intramuscular injection per day for up to 1 month.

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Acthar has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Multiple Sclerosis (MS) as "Pulse Therapy" on a Monthly Basis.** Preliminary data have investigated use of Acthar given as 80 units given intramuscularly (IM) once a day for 3 days once a month.[9] This is not an accepted use of Acthar and more data are needed.

2. **Treatment of Proteinuria in Diabetic Nephropathy.** At this time, limited data are available[10] and Acthar is not established for this use.

3. **Treatment of Nephrotic Syndrome.** The prescribing information for Acthar states that it may be used in an edematous state, such as 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.[1] However, very limited data have studied the use of Acthar, in patients with diagnoses including idiopathic membranous nephropathy (iMN), membranoproliferative glomerulonephritis (MPGN), focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), immunoglobulin A (IgA) nephropathy, class V SLE glomerulonephritis, and monoclonal diffuse proliferative glomerulonephritis.[11-33] A multicenter retrospective case series involving 44 patients did find that proteinuria was reduced in many patients with nephrotic syndrome with Acthar gel.[23] However, this trial had small number of patients involved with the various etiologies, did not use a control group, was retrospective, and did not account that the other concurrent therapy or long-term effects of prior immunosuppressive or cytotoxic therapy may have led to the proteinuria response.[23] Other data in nephrotic syndrome are available regarding use of a synthetic ACTH analog that is available in Europe (tetracosactide [Synacthen® Depot]).[18-22] Limited data from a prospective, open-label trial were published involving 15 patients with resistant glomerular diseases who received Acthar 80 units SC twice weekly for 6 months; most patients had tried previous immunosuppressive therapy and/or steroids.[16] Although some benefits were noted in selected patients (e.g., achievement of partial remission) the authors concluded that controlled studies should be performed against currently available therapies for resistant disease.[16] Two reviews regarding the treatment of iMN notes that experience with ACTH in the US is far too preliminary to consider using this therapy for widespread

use.[12-13] In June 2012, KDIGO published clinical practice guidelines for glomerulonephritis.[11] Many other options besides ACTH are recommended in a variety of scenarios, including children with steroid-sensitive nephrotic syndrome, children with steroid-resistant nephrotic syndrome, MCD in adults, idiopathic FSGS in adults, iMN, and idiopathic MPGN. The guidelines state that the data involving ACTH is of low quality in iMN. The use of ACTH requires further study and data are insufficient to make specific recommendations. In 2013, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) organized a work group of experts to review the 2012 KDIGO guideline and comment on the recommendations in the practice of nephrology in the US.[30] Recommendations regarding Acthar are that ACTH (adrenocorticotrophic hormone) is not recommended as a steroid-like option in children as it has not been studied in this population with steroid-resistant nephrotic syndrome or in steroid-sensitive nephrotic syndrome. Among the treatment of resistant membranous nephropathy in adults, it is stated that the use of ACTH requires further study. The purified porcine ACTH agent approved in the US is a different formulation with alternative dosing compared with the synthetic agent that has been more adequately investigated in Europe. Only small studies have been performed with the US formulation. Data are very preliminary and do not yet support use of this treatment outside clinical research studies. It is not recommended to use ACTH for initial treatment of iMN at this time. Adverse events related to use of ACTH (myopathy, cataracts, hyperglycemia) are not insignificant. Issues that need to be studied with this medication include optimal dosing regimens, rate of relapse, and mechanisms of action.[30] Additionally, guidelines from the American College of Rheumatology (ACR) for the screening, treatment and management of lupus nephritis, published in 2012, do not mention use of Acthar gel.[33]

4. **Dermatomyositis or Polymyositis.** More recent data are limited to a five-patient retrospective case series detailing the effects of Acthar in patients with dermatomyositis and polymyositis.[34,35] Controlled trials are needed before Acthar can be considered an established or recommended therapy. The idiopathic inflammatory myopathies are a group of rare, systemic connective tissue diseases that impact the muscles leading to proximal muscle weakness, muscle enzyme elevations and extramuscular manifestations (e.g., fever, rash), and include diagnoses such as adult polymyositis and dermatomyositis.[35] The initial treatment approach in adult patients include high-dose corticosteroids (prednisone 0.5 to 1 mg/kg per day for 2 to 4 weeks) given with either methotrexate, azathioprine or mycophenolate mofetil. For patients with disease refractory to conventional therapy, agents used include IV methylprednisolone, intravenous immunoglobulin (IVIG), cyclophosphamide, rituximab injection, and cyclosporine.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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## HISTORY

| Type of Revision | Summary of Changes | Date Reviewed |
|---|---|---|
| New Policy | Not applicable | 07/25/2018 |
| Selected revision | Added documentation requirement for multiple sclerosis, treatment of acute exacerbations in adults. Also, revised the policy statement to the standard language. | 10/03/2018 |
| Early annual revision | The criteria regarding the treatment of acute exacerbations of MS in adults were removed. No recent quality data have emerged regarding this condition of use and other agents, such as intravenous methylprednisolone, are preferred in these clinical scenarios. Individual circumstances should be reviewed on a case-by-case basis, as needed. Consistent with formatting changes the Initial Approval/Extended Approval, Duration of Therapy, Labs/Diagnostics, and Waste Management Sections were removed. | 04/10/2019 (effective 7/1/2019) |
| Selected revision | The following criteria changes were made:<br>1. **Infantile Spasms, Treatment:** The criterion was changed from patients < 5 years of age to < 2 years of age. Regarding the requirement of a specialist, an epileptologist was removed from the criteria; the requirement that the medication be prescribed by or in consultation with a neurologist remains. The Dosing section was revised to provide for the maximum dosing (see Policy). | 9/25/2019 |
| Annual revision | No criteria changes. | 03/25/2020 |

MS – Multiple sclerosis.