PRIOR AUTHORIZATION POLICY

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

TAC APPROVAL DATE: 07/25/2018

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. Acthar is also indicated for the treatment of exacerbations of multiple sclerosis (MS) in adults.\(^1\) Acthar is 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).

Acthar is supplied in a 5 mL multi-dose vial containing 80 USP units per mL.\(^1\) For the treatment of infantile spasms, Acthar is administered by intramuscular (IM) injection and the recommended regimen is a daily dose of 150 units/m\(^2\) (divided into twice daily IM injections of 75 units/m\(^2\)) given over a 2-week period. Acthar gel should be gradually tapered over a 2-week period to avoid adrenal insufficiency. For the treatment of acute exacerbations in adults with MS, Acthar is administered by IM or subcutaneous (SC) injection at doses of 80 to 120 units for 2 to 3 weeks. It may be necessary to taper the dose and increase the injection interval to gradually discontinue Acthar. Acthar is contraindicated for intravenous (IV) administration.

Initial approval of Acthar in the US was in 1952.\(^1\) At that time, original approval only required that the medication was safe for human use.\(^2\) Current guidelines, reviews, or position papers from nationally recognized organizations discuss the role of Acthar in infantile spasms\(^3,4\) and MS.\(^5\) The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for glomerulonephritis note that ACTH has a limited role.\(^7\) Other reviews have been published regarding nephrotic syndrome but do not mention use of Acthar\(^8\) or note that experience with the agent is far too preliminary.\(^9\) The recommended authorization criteria address the use of Acthar in infantile spasms and MS exacerbations in adults. Regarding Acthar’s other uses, data and guidelines do not suggest that Acthar has a substantial role in therapy. Further data are needed before use in other areas can be recommended.
**POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of Acthar. The recommended authorization criteria address the use of Acthar in infantile spasms and MS exacerbations in adults. Because of the specialized skills required for evaluation and diagnosis of patients with these conditions, as well as monitoring required for adverse events (AEs) 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.

**Automation:** None.

**Documentation:** In the Acthar Gel PA Policy, documentation is required where noted in the criteria as [documentation required]. Documentation may include, but is not limited to, chart notes and prescription claims records.

**RECOMMENDED AUTHORIZATION CRITERIA**

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

**FDA-Approved Indications**

1. **Infantile Spasms, Treatment.** Approve Acthar for 1 month if the patient meets the following criteria (A and B):
   A) The child is less than 5 years of age; AND
   B) Acthar is prescribed by, or in consultation with, a neurologist or an epileptologist.

   Acthar is indicated as monotherapy for the treatment of infantile spasms in infant and children under 2 years of age.\(^1\) 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.\(^3\) The guidelines note that ACTH is a first-line agent for the short-term treatment of infantile spasms.\(^3\) The Infantile Spasms Working Group (ISWG) published a US consensus report on infantile spasms in 2010.\(^4\) Data regarding ACTH use in infantile spasms were detailed and it was determined that ACTH is an effective first-line therapy for infantile spasms.\(^4\) Published data are also available.\(^10-13\) 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.\(^4\) 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).

2. **Multiple Sclerosis (MS), Treatment of Acute Exacerbations in Adults [documentation required].** Approve Acthar for 1 month if the patient meets the following criteria (A, B, and C):
   A) Acthar is prescribed by, or in consultation with, a neurologist or a physician that specializes in the treatment of MS; AND
   B) The patient meets ONE of the following conditions (i or ii):
      i. The patient cannot use high-dose IV corticosteroids (e.g., methylprednisolone) because IV access is not possible (e.g., difficulty in placing a peripheral IV line); OR
      ii. The patient meets both of the following (a and b):

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\(^{1}\) data reference

\(^{2}\) data reference

\(^{3}\) data reference

\(^{4}\) data reference

\(^{10-13}\) data reference
a) The patient has tried high-dose corticosteroids administered IV (e.g., methylprednisolone 500 to 1,000 mg IV daily for 3 to 5 days) for an acute MS exacerbation/relapse; AND
b) The patient has experienced a severe or limiting adverse effect to the high-dose corticosteroid (e.g., a psychotic reaction); AND
C) The patient is not using Acthar as “pulse therapy” (defined as use on a once monthly or routine basis to prevent MS exacerbations).

Acthar is indicated for the treatment of exacerbations of MS in adults. Acthar has been studied in patients with acute exacerbations of MS and short-term use, usually given IM or SC for 14 or fewer days, led to benefits in signs and symptoms of MS. A double-blind, randomized controlled trial found that ACTH given IM over 14 days had similar efficacy in acute exacerbations of MS as methylprednisolone given as 1 gram IV daily for 3 days. Acute MS exacerbations generally only occur once yearly for those with relapsing forms who are receiving optimal disease-modifying agents. In 2008 the National MS Society published recommendations regarding corticosteroids in the management of MS. High-dose corticosteroids given short-term are the standard of care for the treatment of MS relapses, if needed. The most commonly used agent is methylprednisolone 500 to 1,000 mg given daily as an IV injection for 3 to 5 days with or without a subsequent tapering dose of oral steroids (e.g., prednisone) for 1 to 3 weeks. The steroid most commonly utilized to treat MS relapses is IV methylprednisolone but other options may be appropriate at comparable doses, such as IV dexamethasone. Low dose oral steroids are not generally recommended for the treatment of MS relapses because they are less efficacious. The National MS Society has a document regarding HP Acthar gel. Acthar may have a role in selected patients, such as patients having difficulty receiving IV medication due to poor venous access. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

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. **Use in Patients with Multiple Sclerosis (MS) as “Pulse Therapy” on a Monthly Basis.** Preliminary data have investigated use of Acthar given as 80 units IM once a day for 3 days once a month. This is not an accepted use of Acthar and more data are needed.

2. **Treatment of Proteinuria in Diabetic Nephropathy.** Acthar is being investigated for this use. At this time, limited data are available 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. 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. A multicenter retrospective case series involving 44 patients did find that proteinuria was reduced in many patients with nephrotic syndrome with Acthar gel. This is not an accepted use of Acthar and more data are needed.
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. Other data in nephrotic syndrome are available regarding use of a synthetic ACTH analog that is available in Europe (tetracosactide [Synacthen® Depot]). 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. 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. 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. In June 2012, KDIGO published clinical practice guidelines for glomerulonephritis. 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. 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 regimens 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. AEs 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. 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.

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. 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. 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, Rituxan® (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.
REFERENCES

1. H.P. Acthar® Gel injection for subcutaneous and intramuscular use [-prescribing information]. Bedminster, NJ: Mallinckrodt; April 2018.


Acthar Gel PA Policy


**OTHER REFERENCES UTILIZED**


**HISTORY**

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>TAC Approval Date</th>
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<tbody>
<tr>
<td>Annual revision</td>
<td>No criteria changes</td>
<td>10/04/2017</td>
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<tr>
<td>Selected revision</td>
<td>Documentation is now required to confirm that the patient is treating an acute exacerbation of multiple sclerosis.</td>
<td>07/11/2018</td>
</tr>
<tr>
<td>Early annual revision</td>
<td>No criteria changes</td>
<td>07/25/2018</td>
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TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.

07/25/2018

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