repository corticotropin (Acthar® Gel, Cortrophin™ Gel)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO117

Description

Repository corticotropin injection (Acthar, Cortrophin) gel is an adrenocorticotropic hormone (ACTH) analogue that stimulates the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and other weak androgenic substances.

Length of Authorization

- Initial: One month
- Renewal: One month, total of two courses allowed per lifetime (i.e., one renewal allowed).

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
repository corticotropin injection (Acthar and Acthar Gel SelfJect™) gel	Infantile Spasms (West Syndrome)	80 units/mL vial (400 units/5mL)	Monthly quantity in mL to allow for: 150 u/m^2 daily for two weeks plus a two-week taper as follows: three days' worth of 30 u/m^2, three days' worth of 15 u/m^2, six days' worth of 10 u/m^2
	Multiple sclerosis, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states (serum sickness), ophthalmic diseases, respiratory diseases, edematous state	40 units/0.5 mL or 80 units/mL single dose autoinjector*	1 injection/day
repository corticotropin injection (Cortrophin) gel	Infantile Spasms (West Syndrome)	80 units/mL vial (400 units/5mL)	Monthly quantity in mL to allow for: 150 u/m^2 daily for two weeks plus a two-week taper as follows: three days' worth of 30 u/m^2, three days' worth of 15 u/m^2, six days' worth of 10 u/m^2

**All indications for the Acthar Gel SelfJect™ autoinjector are considered not medically necessary. This product is NOT approved for infantile spasms.*

Initial Evaluation

I. **Repository corticotropin (Acthar vial, Cortrophin) gel** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   B. A diagnosis of one of **Infantile Spasms (West Syndrome)**; **AND**
      1. Member is under two years of age; **AND**
      2. Medication to be used as monotherapy; **AND**
      3. Documentation of recent body surface area; **OR**
         i. Documentation of member's height and weight (needed for dose calculation).

II. Repository corticotropin (Acthar Gel and Acthar Gel SelfJect™, Cortrophin) gel is considered not medically necessary when criteria above are not met and/or when used for the following:
   A. Multiple sclerosis
   B. Rheumatoid arthritis
   C. Psoriatic arthritis
   D. Ankylosing spondylitis
   E. Dermatomyositis/polymyositis
   F. Optic neuritis (40 units daily, also included in investigational section for other doses, see below)
   G. For use in nephrotic syndrome over corticosteroid therapy (also included in investigational section, see below)

III. Repository corticotropin (Acthar Gel and Acthar Gel SelfJect™, Cortrophin) is considered investigational when used for all other conditions, including but not limited to:
   A. In combination with anti-epileptic therapies for the treatment of infantile spasms (West Syndrome)
   B. Ophthalmic conditions and diseases: keratoconjunctivitis sicca, Sjogren's syndrome, dry eye disease, keratitis, iritis, iridocyclitis, uveitis, choroiditis, optic neuritis, etc.
   C. Nephrotic syndrome (NS) and NS due to focal segmental glomerulosclerosis (FSGS) or immunoglobulin A nephropathy (IgAN)
   D. Juvenile rheumatoid arthritis
   E. Lupus erythematosus
   F. Dermatologic conditions: erythema multiforme, Steven's Johnson syndrome
   G. Serum sickness
   H. Sarcoidosis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of one of **Infantile Spasms (West Syndrome)**; **AND**
    A. Member is under two years of age; **AND**
    B. Medication to be used as monotherapy; **AND**
    C. Documentation of recent body surface area; **OR**
        a. Documentation of member's height and weight (needed for dose calculation); **AND**
IV. The member has been previously treated successfully with an initial treatment course of repository corticotropin (Acthar, Cortrophin) gel (i.e., improvement in seizures); **AND**
V. The member has relapsed, and a second course of therapy is warranted; **AND**
VI. The member has not yet received a total of two or more courses of therapy in their lifetime.

Supporting Evidence

I. **Infantile spasms (West Syndrome):** Repository corticotropin (Acthar) gel is an ACTH analogue that acts similarly to corticosteroids and was FDA-approved for infantile spasms in 2010. Data from several randomized controlled trials are available to support safety and efficacy. One clinical trial showed superiority over prednisone in the proportion of patient responders to therapy. Other studies directly comparing therapy to corticosteroids did not determine statistical superiority of repository corticotropin (Acthar) gel. Although data for superiority of repository corticotropin (Acthar) gel over corticosteroids are conflicting, there is insufficient evidence to support that corticosteroids could be more effective than repository corticotropin (Acthar) gel. Guidelines recommend repository corticotropin (Acthar) as the mainstay therapy.
    - Infantile spasms are characterized as epileptic spasms that appear in infancy and early childhood. The majority of patients will present before seven months of age, and the condition is associated with electroencephalographic pattern of hypsarrhythmia. This medication has been evaluated and is only FDA-approved for patients under two years of age. In patients older than two years, alternative cost-effective treatment options should be considered.
    - In clinical practice, repository corticotropin (Acthar) gel has been utilized at a variety of doses. The FDA-approved dose (which has also been evaluated in several clinical trials) is as follows: 150 units/m^2 daily (divided between twice daily) for two weeks plus a two-week taper: three days each of 30 units/m^2, 15 units/m^2, 10 units/m^2, followed by 10 units/m^2 every other day for six days. The last six days of therapy equates to total of

three additional days of 10 units/m^2 (equating to six full days of the 10 units/m^2 dose). Several studies have evaluated differing dosing regimens, including lower doses. In the event under dosing is prescribed relative to the FDA-approved dose, this regimen should be allowed given some evidence to indicate that lower doses may be as effective as that FDA-approved. Repository corticotropin (Acthar) gel has been evaluated in clinical trials using 150 units/m^2 for three weeks then a taper for three more weeks; however, this higher dose group did not show superior efficacy to lower doses. Similar rates of response and relapse occurred; thus, at this time there is no evidence to support need for a longer than two-week duration of 150 units/m^2 per day.

- Duration of initial therapy with treatment and taper is four weeks. Response is expected in the first few weeks. There is lack of evidence to support extended use of therapy; however, a second course of therapy may be appropriate for patients that relapse and require retreatment. Lack of response (i.e., number/severity of spasms) on first treatment course signals an alternative regimen should be utilized for retreatment; thus, response to the initial therapy course is required. Long-term safety is similar to corticosteroids: cardiac, ocular, mood, sleep, skin concerns, etc.
- Repository corticotropin (Cortrophin) gel is not FDA-approved for the indication of infantile spasms; however, is not expected to have any clinical differences. This is a more cost-effective treatment option, and when other criteria are met for the indication of infantile spasms, Cortrophin use is covered under the specifications listed above (e.g., QLL, etc.). ANI Pharmaceuticals received FDA-approval of Purified Cortrophin gel in November 2021, in efforts to support broader and more cost-effective access to corticotropin products.

II. Repository corticotropin (Acthar) gel was FDA-approved in 1952 and Cortrophin gel was approved in 1954 for the treatment of inflammatory conditions prior to current FDA standards, and the indications were grandfathered into the labels; however, corticotropin products have not demonstrated evidence for safety and efficacy, or medical necessity over corticosteroids, for the majority of the labeled indications. Furthermore, the cost has increased significantly over the past few decades: $36 per vial in 2001; in 2022, $49,750 per vial for Acthar and $38,200 for Cortrophin. The evidence for indications outside of infantile spasms and multiple sclerosis (MS) are absent, are low quality and/or lacking ability to conclude efficacy and safety alone or in comparison to more cost-effective therapies (e.g., corticosteroids). Data to support efficacy for indications other than infantile spasms are absent from the prescribing information label. The manufacturer of Acthar, Mallinckrodt has funded several Phase 4 clinical trials in recent years in efforts to provide support for the approved indications; however, by in large these clinical trials are insufficient to support the safety and efficacy and/or medical necessity over other therapies.

Investigational or Not Medically Necessary Uses*

**Disclaimer: In the event an approval is granted for corticotropin for any condition outside of infantile spasms (West Syndrome), Acthar will only be allowed after a sufficient trial and failure of Cortrophin, supported with documentation and rationale.*

I. Repository corticotropin (Acthar, Cortrophin) (ACTH) gel is considered not medically necessary for the following conditions:
   A. Multiple sclerosis: At this time, it is unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroids, given lack of quality trials and trials with consistent results showing superiority; however, ACTH gel is more costly than other therapies that could be utilized. Given these factors ACTH gel is not medically necessary for MS and is not covered. Furthermore, choice of or success of therapy in acute MS exacerbation has not been correlated with improved or superior long-term outcomes, further reducing the necessity of ACTH gel for this condition.
   B. Rheumatoid arthritis, psoriatic arthritis, dermatomyositis/polymyositis, ankylosing spondylitis: ACTH gel has been evaluated in Phase 4, randomized, placebo-controlled withdrawal studies for these conditions in addition to several lesser quality trials. In some trials, therapy was superior to placebo for disease response; however, this medication has not been directly compared to NSAIDS, the majority of systemic corticosteroids, conventional synthetic DMARDs, specialty DMARDS, and biologic therapies. Numerous other medications have strong evidence for safety and efficacy, all of which are more cost-effective. At this time, it is unproven if ACTH gel is more likely to produce similar therapeutics results or is superior to other therapies; however, ACTH gel is more costly than other therapies that could be utilized. Furthermore, ACTH gel is not recognized as an appropriate therapy per guidelines or standard practice; thus, is considered not medically necessary and is not covered.
   C. Optic neuritis (also considered experimental and investigational, see below): ACTH gel was evaluated in one RCT vs. placebo, where 40 units daily for 30 days did not provide significant changes over placebo in visual acuity and visual field scores. Given that it is not known if therapy improves therapeutic outcomes at this dose, ACTH gel is considered not medically necessary and is not covered.
   D. Nephrotic syndrome: superiority of ACTH gel over corticosteroids and other treatment options for this condition has not been demonstrated; certain trials have shown lack of benefit over placebo therapy and one clinical trial showed noninferiority to methylprednisolone. At this time, it is unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroid therapies; however, ACTH gel is more costly than other therapies that could be utilized. Given these factors ACTH gel is not medically necessary and is not covered.

II. Repository corticotropin (Acthar, Cortrophin) gel has not been sufficiently studied for safety and efficacy, and are considered experimental and investigational, for the following conditions or settings below:
    A. In combination with anti-epileptic therapies for the treatment of infantile spasms (West Syndrome): ACTH gel has only been evaluated as monotherapy for the treatment of infantile spasms. There is unknown safety and efficacy when utilized for other anti-epileptic medications. When combination therapy is indicated vigabatrin plus corticosteroids may be considered as available evidence for efficacy and safety.
    B. Systemic lupus erythematosus (SLE): Evaluated in a single-arm, open-label, four-week trial in 10 patients. This trial does not provide any certainty in the benefit of ACTH gel for SLE given the significant trial biases: subjective outcomes in an open-label trial, no comparator to be able to determine extent of benefit over placebo (if any), few patients evaluated, and concomitant medications which may have impacted/influenced the changes.
    C. Optic neuritis (ON) (higher doses): Evaluated in a single-arm, open-label, 2-week trial at a starting dose of 80 units daily in 24 patients with ON. This trial does not provide any certainty in the benefit of therapy for ON given the significant biases in the trial: subjective outcomes in an open-label trial, few patients evaluated, short trial duration, and patients were on background therapies at the start of the trial, with no washout period. Results/conclusions seen in this assessment may not be attributable to ACTH gel.
    D. Sarcoidosis: Evaluated for sarcoidosis in one retrospective medical record review, on provider assessment of “patients’ health status”. The trial showed that use of concomitant medications such as glucocorticoids decreased with use of ACTH gel. This trial does not provide any certainty in the benefit of therapy for this condition given the significant biases: retrospective trial design, subjective and invalidated outcomes in a nonblinded trial, most patients were on background therapies. Results/conclusions seen in this assessment may not be attributable to ACTH gel.
    E. Nephrotic Syndrome (NS), including but not limited to those with FSGS: Evaluated in retrospective case series; a prospective, open-label, single arm trial, a randomized noninferiority trial vs. methylprednisolone with cytotoxic therapies; a randomized, placebo-controlled trial; a dose comparison trial; and one Cochrane systematic review evaluated in one retrospective case series in 44 patients (15 patients had FSGS). Data are heavily conflicting, none of which strongly point to medication benefit. For example, one of the randomized controlled trials showed no substantial differences compared to no therapy and the trial was ended early for no benefit. In the noninferiority trial, similar responses were seen to methylprednisolone. The Cochrane review determined lack of sufficient data to draw conclusions of efficacy and safety. The collection of data does not provide certainty of benefit of therapy for NS, is considered experimental and investigational, and is not covered by the health plan. At this time, it is also unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other

corticosteroid therapies; however, ACTH gel is more costly than other therapies that could be utilized. Thus, ACTH gel is also not medically necessary over corticosteroids and is not covered.

i. NS due to immunoglobulin A nephropathy (IgAN): ACTH gel was evaluated in a single-arm, open-label pilot study in 19 patients. This trial does not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to small number of patients in the trial, lack of comparator arm, and the majority of outcomes were unchanged at follow-up.

F. Ophthalmic conditions and diseases, including but not limited to: keratoconjunctivitis sicca, Sjogren's syndrome, dry eye disease, keratitis, iritis, iridocyclitis, uveitis, choroiditis:

i. Keratitis/dry eye disease: ACTH gel was evaluated in a single-arm, open-label study in 35 patients with keratitis. The trial observed 12-point change in IDEEL score for 17 patients (50%) with severe keratitis. ACTH gel was also evaluated in a single-arm, open-label pilot study in dry eye disease in 15 patients. The study evaluated the SANDE questionnaire for patient reported improvement; however, these trials do not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to subjective outcomes in an open-label trial, lack of comparator, the small number of patients evaluated, and background or concomitant therapies may not have been reported so any results or conclusions may not be attributable to ACTH gel. Furthermore, the SANDE score is not a validated measurement tool for clinically meaningful change in dry eye comfort or symptom improvement.

1. Alternative therapies and management strategies include, but may not be limited to: avoidance of offending medications, environmental management, moisture conserving eyewear, ocular lubricants, artificial tears and preservative-free artificial tears (gels, ointments, drops), ophthalmic cyclosporine (generic, Restasis, Cequa), ophthalmic lifitegrast (Xiidra), nasal varenicline (Tyrvaya), punctal plugs or occlusion, topical steroids, therapeutic contact lenses, autologous serum tear preparations.

ii. Uveitis: ACTH gel has been evaluated for uveitis in one retrospective trial evaluating medical record data of provider assessment on patients' health status for 91 patients. Trial conclusions were that provider reported improved patient status; however, this trial does not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to subjective outcomes in an open-label trial, lack of comparator, the small number of patients evaluated, and background or concomitant therapies were utilized by 100% of patients (including steroid eye drops, oral steroids, intraocular steroids, and non-steroid eye drops) so any results or conclusions may not be attributable to ACTH gel.

III. Juvenile rheumatoid arthritis
IV. Dermatologic conditions: erythema multiforme, Steven's Johnson syndrome
V. Serum sickness
VI. Sarcoidosis

Appendix

I. Methods to calculate body surface area include, but are not limited to the Mosteller method: BSA (m^2) = Square root ((Ht (cm) x Wt (kg))/3600)

References

1. Acthar Gel [Prescribing Information]. Mallinckrodt ARD LLC. Bedminster, NJ. February 2024.
2. Purified Cortrophin Gel [Prescribing Information]. ANI Pharmaceuticals, Inc. Baudette, MN. November 2021.
3. Tran KA, Harrod C, Bourdette DN, Cohen DM, Deodhar AA, Hartung DM. Characterization of the clinical evidence supporting repository corticotropin injection for fda-approved indications: a scoping review. JAMA Intern Med. 2022;182(2):206-217.
4. Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (Acth) versus prednisone for infantile spasms: a prospective, randomized, blinded study. Pediatrics. 1996;97(3):375-379.
5. Hrachovy RA, Frost JD, Glaze DG. High-dose, long-duration versus low-dose, short-duration corticotropin therapy for infantile spasms. The Journal of Pediatrics. 1994;124(5):803-806.
6. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms: report of the guideline development subcommittee of the american academy of neurology and the practice committee of the child neurology society. Neurology. 2012;78(24):1974-1980.
7. Nelson GR. Management of infantile spasms. Transl Pediatr. 2015;4(4):260-270.
8. National Multiple Sclerosis Society. Managing Relapses. Available at: https://www.nationalmssociety.org/Treating-MS/Managing-Relapses#section-2
9. Multiple Sclerosis Association of America. Treating Multiple Sclerosis Relapse. October 2017. Available at: https://mymsaa.org/ms-information/treatments/relapses/
10. Barnes MP, Bateman DE, Cleland PG, et al. Intravenous methylprednisolone for multiple sclerosis in relapse. Journal of Neurology, Neurosurgery & Psychiatry. 1985;48(2):157-159.
11. Milanese C, Mantia LL, Salmaggi A, et al. Double-blind randomized trial of acth versus dexamethasone versus methylprednisolone in multiple sclerosis bouts. ENE. 1989;29(1):10-14.
12. Thompson AJ, Kennard C, Swash M, et al. Relative efficacy of intravenous methylprednisolone and ACTH in the treatment of acute relapse in MS. Neurology. 1989;39(7):969-969.
13. Prevoo MLL, Van'T Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LBA, Van Riel PLCM. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis: MODIFIED DISEASE ACTIVITY SCORE. Arthritis & Rheumatism. 1995;38(1):44-48.
14. Fiechtner JJ, Montroy T, June J. A single-site, investigator initiated open-label trial of H.P. Acthar® Gel (repository corticotropin injection) an adrenocorticotropic hormone (ACTH) analogue in subjects with moderately to severely active psoriatic arthritis (PsA). J Dermatol Res Ther. 2016;2(5):1-7.
15. B.P. Wordsworth, M. J. Pearcy, A. G. Mowat, In-patient regime for the treatment of ankylosing spondylitis: an appraisal of improvement in spinal mobility and the effects of corticotrophin. *Rheumatology*. 1984;23(1):39-43.
16. Fleischmann R, Furst DE, Connolly-Strong E, Liu J, Zhu J, Brasington R. Repository corticotropin injection for active rheumatoid arthritis despite aggressive treatment: a randomized controlled withdrawal trial. Rheumatol Ther. 2020;7(2):327-344.

17. Aggarwal R, Marder G, Koontz DC, Nandkumar P, Qi Z, Oddis CV. Efficacy and safety of adrenocorticotropic hormone gel in refractory dermatomyositis and polymyositis. Ann Rheum Dis. 2018;77(5):720-727.
18. Fiechtner JJ, Montroy T. Treatment of moderately to severely active systemic lupus erythematosus with adrenocorticotropic hormone: a single-site, open-label trial. Lupus. 2014;23(9):905-912.
19. Chopra I, Qin Y, Kranyak J, et al. Repository corticotropin injection in patients with advanced symptomatic sarcoidosis: retrospective analysis of medical records. Ther Adv Respir Dis. 2019;13:1753466619888127. doi:10.1177/1753466619888127.
20. Michelle A. Hladunewich, Daniel Cattran, Laurence H. Beck, Ayodele Odutayo, Sanjeev Sethi, Rivka Ayalon, Nelson Leung, Heather Reich, Fernando C. Fervenza, A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (H.P. Acthar® Gel) in nephrotic syndrome due to idiopathic membranous nephropathy, Nephrology Dialysis Transplantation, Volume 29, Issue 8, August 2014, Pages 1570–1577
21. Wang C shi, Travers C, McCracken C, et al. Adrenocorticotropic hormone for childhood nephrotic syndrome. CJASN. 2018;13(12):1859-1865.
22. Wirta D, McLaurin E, Ousler G, Liu J, Kacmaz RO, Grieco J. Repository corticotropin injection (Acthar® Gel) for refractory severe noninfectious keratitis: efficacy and safety from a phase 4, multicenter, open-label study. Ophthalmol Ther. 2021;10(4):1077-1092.
23. Grubbs JR, Tolleson-Rinehart S, Huynh K, Davis RM. A review of quality of life measures in dry eye questionnaires. Cornea. 2014;33(2):215-218.
24. Nelson WW, Lima AF, Kranyak J, et al. Retrospective medical record review to describe use of repository corticotropin injection among patients with uveitis in the United States. J Ocul Pharmacol Ther. 2019;35(3):182-188.
25. Bryan MS, Sergott RC. Changes in visual acuity and retinal structures following repository corticotropin injection (RCI) therapy in patients with acute demyelinating optic neuritis: improvement in low contrast visual acuity in both affected and contralateral eyes in a single-armed open-label study. J Neurol Sci. 2019;407:116505. doi:10.1016/j.jns.2019.116505.
26. Alhamad T, Manllo Dieck J, Younus U, et al. ACTH gel in resistant focal segmental glomerulosclerosis after kidney transplantation. Transplantation. 2019;103(1):202-209.
27. Hladunewich MA, Cattran D, Beck LH, et al. A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (Acthar® Gel) in nephrotic syndrome due to idiopathic membranous nephropathy. Nephrol Dial Transplant. 2014;29(8):1570-1577.
28. Madan A, Mijovic-Das S, Stankovic A, Teehan G, Milward AS, Khastgir A. Acthar Gel in the treatment of nephrotic syndrome: a multicenter retrospective case series. BMC Nephrol. 2016;17:37.
29. Zand L, Canetta P, Lafayette R, et al. An open-label pilot study of adrenocorticotrophic hormone in the treatment of IgA nephropathy at high risk of progression. Kidney Int Rep. 2020;5(1):58-65.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Acthar Gel SelfJect™ to policy/QL table.	09/2024
Policy criteria updated for infantile spasms indication: removal of congenital infection rule out, addition of body surface (or height and weight) requirement for dose calculation. Change of renewal criteria to check that patients still meet initial requirements and that member has had a response to therapy that would predict response with a retreatment. Criteria updated to allow for maximum of two courses per lifetime. Supporting evidence updated for infantile spasms, not medically necessary and experimental and investigational designations and information added for supporting evidence. Addition of Cortrophin to policy. Formatting updates.	06/2022

Policy created	11/2019