Corticotropin-ACTH:

Acthar® Gel (repository corticotropin injection)
Cortrophin™ Gel (repository corticotropin injection)
(Intramuscular)

Document Number: IC-0003

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I. Length of Authorization

Coverage will be provided for 1 month and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Acthar Gel 80 units/mL injection (5 mL multi-dose vial): 4 vials per 28 days
- Cortrophin Gel 80 units/mL injection (5 mL multi-dose vial): 4 vials per 28 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- 35 billable units (1377 USP units) every 28 days

III. Initial Approval Criteria [1,2,5-18,47-52]

Infantile Spasms (West Syndrome) (Acthar † Φ; Cortrophin ‡[48-53])

- Patient is under 2 years of age; **AND**
- Clinical documentation indicating patient has a diagnosis of infantile spasms (West Syndrome); **AND**
- Must be used as monotherapy; **AND**
- Documentation that patient does not have a suspected congenital infection

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

Use of repository corticotropin injection for indications including, but not limited to, those additionally listed in the product labeling are not supported by substantial clinical evidence.
Repository Corticotropin Injection was originally approved by the U.S. Food and Drug Administration (FDA) in 1952 as HP ACTH and in 1954 as Cortrophin, for a variety of disorders and diseases that at the time were thought to benefit from steroid mediated immunosuppression. The initial approval of H.P. ACTH and CORTROPHIN gels occurred prior to the Kefauver-Harris amendment to the Federal Food, Drug and Cosmetic Act of 1962, which introduced the requirement of "substantial evidence" of two adequate and well controlled trials. At the time of the original approval drug manufacturers only had to show the drug was safe for use in humans. The original data included case reports from a few physicians describing patients with conditions originally treated with adrenocorticotropic hormone powder that were transferred to treatment with the approved product and gave dosing guidance for treatment of these individual conditions. These data would be grossly inadequate to support approval of a new drug or new indications by the Agency under current standards requiring evidence from adequate and well-controlled clinical trials. A Drug Efficacy Study Implementation (DESI) review of corticotrophin injection (Acthar NDA 022432) was initiated in 1971 and finalized in 1977.[4] Cortrophin was approved via sNDA November 2021.

IV. Renewal Criteria [1,2]

Authorizations can be renewed based on the following criteria:

- Patient continues to meet indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as indicated by resolution of symptoms and/or normalization of laboratory tests; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe infections, severe electrolyte imbalances, gastric bleeding or ulcer, hypertension, hypokalemia, severe depression, frank psychotic manifestations, posterior subcapsular cataracts, glaucoma, anaphylaxis, etc.

V. Dosage/Administration [1,4,47-50]

Indication	Dose
Infantile Spasms	Administer 75 units/m^2 intramuscularly given twice daily for 2 weeks, then taper the dose over a 2 week period (e.g., 30 units/m^2 in the morning for 3 days; 15 units/m^2 in the morning for 3 days; 10 units/m^2 in the morning for 3 days; and 10 units/m^2 every other morning for 6 days).

VI. Billing Code/Availability Information

HCPCS code:

- J0800 – Injection, corticotropin, up to 40 units; up to 40 units = 1 billable unit (applicable to Acthar only)
- J3490 – Unclassified Drugs (applicable to Cortrophin ONLY)

NDC:

- H.P. Acthar Gel 80 units/mL (5 mL multi-dose vial): 63004-8710-xx
- Purified Cortrophin Gel 80 USP units/mL (5 mL multi-dose vial): 62599-0860-xx

VII. References

1. Acthar Gel [package insert]. Bedminster, NJ; Mallinckrodt ARD, LLC.; October 2021. Accessed December 2021.
2. Purified Cortrophin Gel [package insert]. Baudette, MN; ANI Pharmaceuticals, Inc.; November 2021. Accessed December 2021.
3. Center for Drug Evaluation and Research. APPLICATION NUMBER: 022432Orig1s000. Approval Package. U. S. Food and Drug Administration. Washington, DC.
4. Center for Drug Evaluation and Research. APPLICATION NUMBER: 022432Orig1s000. Other Review(s). U. S. Food and Drug Administration. Washington, DC.
5. Go, C.Y., Mackay, M.T., Weiss, S.K. 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;1974-1980.
6. Hussain SA, Shinnar S, Kwong G, et al. Treatment of infantile spasms with very high dose prednisolone before high dose adrenocorticotropic hormone. Epilepsia. 2014 Jan;55(1):103-7. doi: 10.1111/epi.12460. Epub 2013 Nov 8.
7. Hrachovy RA, Frost JD, Glaze DG et al. High-dose, long-duration versus low-dose, short duration corticotropin therapy for infantile spasms. J Pediatr 1994;124:803-806.
8. Kivity S, Lerman P, Ariel R, et al. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. Epilepsia. 2004 Mar;45(3):255-62.
9. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010 Oct;51(10):2175-89.
10. M. T. Mackay, S. K. Weiss, T. Adams-Webber, et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology 2004;62;1668-81.
11. Hussain S, et al "Treatment of infantile spasms with very high dose prednisolone before high dose ACTH" AES 2012; Abstract 1.247.
12. Baram TZ, Mitchell WG, Tournay A et al. High-dose corticotropin (ACTH) versus prednisone for infantile spasm: A prospective, randomized, blinded study. Pediatrics. 1996 Mar; 97(3): 375–379.
13. Hrachovy RA, Frost JD, Kellaway P, et al. Double-blind study of ACTH vs. prednisone therapy in infantile spasms. J Pediatr 1983 Oct; Volume 103: pp 641-5.
14. Snead OC, Benton WJ, Myers JG. ACTH and prednisone in childhood seizure disorders. Neurology 1983; Volume 33: pp 966.
15. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. Epilepsia Dec1997; 38:1270-4.
16. Cossette P, Riviello J, Carmant L. ACTH versus vigabatrin therapy in infantile spasms: A retrospective study. Neurology 12 May 1999; Volume 52: 1691-1694.
17. Grasntrom ML, Gaily E, Liukkonen E, et al. Treatment of infantile spasms: results of a population-based study with vigabatrin as the first drug for spasms. Epilepsia 1999 July; Volume 40: pp 950-7.

18. Appleton RE, Peters AC, Mumford JP, et al. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. Epilepsia 1999 Nov; Volume 40; pp 1627-33.
19. Gettig J, Cummings JP, Matuszewski K. H.P. Acthar Gel and Cosyntropin Review: Clinical and Financial Implications. P T. 2009 May;34(5):250-257.
20. Philbin M, Niewoehner J, Wan G. Clinical and Economic Evaluation of Repository Corticotropin Injection: A Narrative Literature Review of Treatment Efficacy and Healthcare Resource Utilization for Seven Key Indications. Adv Ther. 2017; 34(8): 1775–1790.
21. 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 Jul;39(7):969-71.
22. Abbruzzese G, Gandolfo C, Loeb C. "Bolus" methylprednisolone versus ACTH in the treatment of multiple sclerosis. The Italian Journal of Neurological Sciences, 1983, Volume 4, Number 2, Page 169.
23. National Medical Advisory Board of the National Multiple Sclerosis Society. Expert Opinion Paper: Recommendations Regarding Corticosteroids in the Management of Multiple Sclerosis. US Neurology, 2008;4(1):22-24.
24. National Clinical Guideline Centre. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 36 p. (Clinical guideline; no. 186).
25. Citterio A, La Mantia L, Ciucci G, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD001331.
26. Simsarian JP, Saunders C, Smith DM. Five-day regimen of intramuscular or subcutaneous self-administered adrenocorticotropic hormone gel for acute exacerbations of multiple sclerosis: A prospective, randomized, open-label pilot trial. Drug Des Devel Ther. 2011;5:381-389.
27. Cortese I, Chaudhry V, So Y, Cantor F, Cornblath D, Rae-Grant A. Evidence-based guideline update: Plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011:76(3):294.
28. Milanese C, La Mantia L, Salmaggi A, et al. Double-blind randomized trial of ACTH versus dexamethasone versus methylprednisolone in multiple sclerosis bouts. Clinical, cerebrospinal fluid and neurophysiological results. Eur Neurol 1989;29(1):10-4.
29. Filippini G, Brusaferri F, Sibley WA, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Cochrane Database Syst Rev. 2000;(4):CD001331.
30. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney inter., Suppl. 2012; 2: 139–274.
31. Wang C, Travers C, McCracken C, et al. Adrenocorticotropic Hormone for Childhood Nephrotic Syndrome. CJASN December 2018, 13 (12) 1859-1865.

32. Lombel RM, Hodson EM, Gipson DS. Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO. Pediatr Nephrol 2013;28:409-14.
33. Bomback AS, Tumlin JA, Baranski J, et al. Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel. Drug Des Devel Ther. 2011;5:147-153.
34. Madan A, Mijovic-Das S, Stankovic A, et al. Acthar gel in the treatment of nephrotic syndrome: a multicenter retrospective case series. BMC Nephrol. 2016; 17:37.
35. Bomback AS, Canetta PA, Beck LH Jr, et al. Treatment of resistant glomerular diseases with adrenocorticotropic hormone gel: a prospective trial. Am J Nephrol. 2012; 36(1):58-67.
36. Chen Y, Schieppati A, Cai G, et al. Immunosuppression for membranous nephropathy: a systematic review and meta-analysis of 36 clinical trials. Clin J Am Soc Nephrol. 2013; 8(5):787-796.
37. Watson MJ. Membranous glomerulopathy and treatment with Acthar® : a case study. Int J Nephrol Renovasc Dis. 2013; 6:229-232.
38. Tumlin JA, Galphin CM, Rovin BH. Advanced diabetic nephropathy with nephrotic range proteinuria: A pilot study of the long-term efficacy of subcutaneous ACTH gel on proteinuria, progression of CKD, and urinary levels of VEGF and MCP-1. J Diabetes Res. 2013;2013:489869.
39. Hogan J, Bomback AS, Mehta K, et al. Treatment of idiopathic FSGS with adrenocorticotropic hormone gel. Clin J Am Soc Nephrol. 2013; 8(12): 2072.
40. Hladunewich MA, Cattran D, Beck LH, et al. A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone in nephrotic syndrome due to idiopathic membranous nephropathy. Nephrol Dial Transplant. 2014 Aug;29(8):1570-7.
41. Hogan J, Radhakrishnan J. The treatment of minimal change disease in adults. J Am Soc Nephrol 2013;24:702-11.
42. Bertsias GK, Tektonidu M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and pediatric lupus nephritis. Ann Rheum Dis 2012;71:1771-82.
43. Fiechtner J, 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.
44. Levine T. Treating refractory dermatomyositis or polymyositis with adrenocorticotropic hormone gel: A retrospective case series. Drug Des Devel Ther. 2012;6:133-139.
45. Baughman RP, Sweiss N, Keijsers R, et al. Repository corticotropin for chronic pulmonary sarcoidosis. Lung. 2017; 195(3):313-322.
46. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol 2011;65:137-74.
47. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. Int J Dermatol 2012;51:889-902.
48. Lexicomp. Corticotropin (pituitary) (AHFS DI (adult and pediatric)). Accessed October 12, 2021. [Database]. https://online.lexi.com

49. Clinical Pharmacology. Corticotropin, ACTH (all populations monograph). [Database]. https://www.clinicalpharmacology.com/
50. MicroMedex DRUGDEX. Corticotrophin. Accessed October 12, 2021. [Database]. http://www.micromedexsolutions.com/
51. Lexicomp. Corticotropin (Lexi-Drugs). [Database]. https://online.lexi.com.
52. Knupp KG, Coryell J, Nickels KC, et al. Response to treatment in a prospective national infantile spasms cohort. Ann Neurol. 2016;79(3):475-484.
53. Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. Epilepsia. 2015;56(8):1185-1197.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
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

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs) and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto Government Benefit Administrators, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC