MEDICAL POLICY

POLICY TITLE	REPOSITORY CORTICOTROPIN INJECTION (H.P. ACTHAR GEL)
POLICY NUMBER	MP-2.162

Original Issue Date (Created):	**May 10, 2011**
Most Recent Review Date (Revised):	**March 25, 2014**
Effective Date:	**June 1, 2014**

I. POLICY

Note: H.P.Acthar Gel (Repository Corticotropin Injection) does not require pre-authorization.

H.P. Acthar Gel (repository corticotropin injection) is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age. H.P. Acthar Gel is also indicated for the treatment of exacerbations of multiple sclerosis (MS) in adults.

Infantile spasms

H.P. Acthar Gel is **medically necessary** for members who meet the following criteria:

- A diagnosis of infantile spasms and less than 2 years of age.
- Does not have a suspected congenital infection
- Has shown substantial clinical benefit if currently receiving therapy.

Approval for coverage will be provided for 6 months.

Multiple Sclerosis

H.P. Acthar Gel for exacerbations of multiple sclerosis is **medically necessary** for members who meet the following criteria:

- None of the following contraindications:
    - scleroderma, osteoporosis, systemic fungal, infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin

- Has tried one of the following standard therapies of multiple sclerosis:
    - Avonex (interferon beta-1a) , Betaseron (interferon beta-1b), Extavia (interferon beta-1b), Rebif (interferon beta-1a), Copaxone (glatiramer acetate), Gilenya (fingolimod), Aubagio (teriflunomide), Tysabri (natalizumab)
- Tried and failed or is intolerant to parenteral corticosteroids or has poor intravenous access.

H.P. Acthar Gel is not recommended in the following situations:

- Has received or will receive a live or live attenuated vaccine within 6 weeks of H.P. Acthar Gel administration.
- Does not meet the conditions listed above.

Cross-reference

MP-2.103 Off-Label Use of Prescription Drugs

II. PRODUCT VARIATIONS

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[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N]	Capital Cares 4 Kids	[N]	Indemnity
[N]	PPO	[N]	SpecialCare
[N]	HMO	[N]	POS
[N]	SeniorBlue HMO	[Y]	FEP PPO*
[N]	SeniorBlue PPO		

* Step therapy requiring a trial of self-administered therapy or oral medication does not apply.

**Refer to FEP Medical Policy Manual MP-5.08.10 H.P. Acthar Gel. The FEP Medical Policy manual can be found at: www.fepblue.org

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III. DESCRIPTION/BACKGROUND

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Repository corticotropin intramuscular or subcutaneous injection has primarily been used for treating infantile spasms (West syndrome). It has also been investigated for diagnostic testing of adrenocortical function and for treating a variety of other conditions.

Repository corticotropin injection (H.P. Acthar® gel, Questcor Pharmaceuticals, Union City, CA) is a purified, sterile preparation of the natural form of adrenocorticotropic hormone (ACTH) in gelatin to provide a prolonged release after intramuscular or subcutaneous injection. ACTH is produced and secreted by the pituitary gland; H.P. Acthar gel uses ACTH obtained from porcine pituitaries. ACTH works by stimulating the adrenal cortex to produce cortisol, corticosterone, and a number of other hormones.

H.P. Acthar gel was approved by the U.S. Food and Drug Administration (FDA) in 1952, before there was a requirement that companies provide clinical evidence of efficacy. The product label states that Acthar gel is indicted for a number of conditions, listed below.

According to the prescribing information (i.e. product label), repository corticotropin injection may be used in the treatment of the following conditions (1):
1.1 Infantile Spasms in infants and children younger than 2 years of age.
1.2 Multiple Sclerosis: Treatment of acute exacerbations of multiple sclerosis in adults. (indication added in 1978).
1.3 Rheumatic Disorders: Adjunctive therapy for patients with acute episodes or exacerbations of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis.
1.4 Collagen Diseases: Treatment of selected cases of systemic lupus erythematous and systemic dermatomyositis.
1.5 Dermatologic Diseases: Treatment of severe erythema multiforme and Stevens-Johnson syndrome.
1.6 Allergic States: Treatment of serum sickness.
1.7 Ophthalmic Diseases: Treatment of severe acute and chronic allergic and inflammatory processes including optic neuritis, keratitis and iritis.
1.8 Respiratory Diseases: Treatment of symptomatic sarcoidosis)
1.9 Edematous State: Treatment of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or due to lupus erythematosus.

Among the above indications, repository corticotrophin injection is best known for the treatment of infantile spasms. This is a rare epileptic disorder of infancy (90% of cases are diagnosed in the first year of life). When infantile spasms are accompanied by neurodevelopmental regression and electroencephalogram (EEG) findings of hypsarrhythmia, the condition is known as West syndrome. Vigabatrin oral solution is another available treatment for infantile spasms.

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Multiple sclerosis (MS) is a chronic disease of the nervous system which affects young and middle-aged adults. A disruption in the ability of the nerves to conduct electrical impulses to and from the brain produces the many symptoms of MS which can lead to permanent disability. Corticosteroids are taken to reduce the inflammation caused by these disruptions.

Diagnostic testing of adrenocortical function, known as the ACTH test, is typically done with synthetic ACTH. Synthetic ACTH products have been approved by the FDA for this purpose. Unlike previous versions of the H.P. Acthar product label, an updated label issued in 2010, did not mention the use of repository corticotropin injection for diagnostic testing of adrenocortical function.

A synthethic derivative of ACTH is commercially available outside of the United States (under the tradenames Cortosyn and Synacthen) but it is not approved by the FDA for any of the conditions currently included in the H.P. Acthar gel FDA-approved label. In addition, a depot formulation of ACTH (Synacthen Depot) is available through a compassionate-use program through the specialty pharmacy Caligor Rx in New York. In June 2013, Questcor Pharmaceuticals announced that they acquired the rights to market Synacthen in the United States, once FDA approval is obtained.

Repository corticotropin injection has potential adverse effects similar to those that occur with steroid medication such as elevated blood pressure, decrease in bone density, new infections or activation of previous infection, and overproduction of cortisol, which can cause symptoms of Cushing's syndrome.

Regulatory Status

H.P. Acthar gel (Questcor Pharmaceuticals) was approved by the FDA in 1952. The product label states that Acthar gel is indicted for 19 conditions, including infantile spasms. Contraindications for use of this agent include scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin. Unlike previous versions of the product label, an updated label issued in 2010, did not include the use of repository corticotropin injection for diagnostic testing of adrenocortical function

IV. RATIONALE

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Infantile spasms

In 2013, Hancock and colleagues published an updated Cochrane review on medication treatment of infantile spasms. (2) The authors identified 18 randomized controlled trials (RCTs) investigating a total of 12 different medications. The overall quality of studies was deemed to be poor i.e., fewer than half the study reported the method of randomization, and only 2 studies had

more than 100 participants. A total of 5 studies compared treatment with adrenocorticotropic hormone (ACTH) to another medication. The review authors did not differentiate between synthetic and natural forms of ACTH. Two studies compared ACTH to vigabatrin (total sample sizes 9 and 42, respectively), 2 compared ACTH to prednisone (n=29 and 24, respectively), and 1 study with 52 participants compared ACTH to nitrazepam. A 6th study compared vigabatrin and ACTH in a subset of patients. Dosages and treatment regimens varied. The authors conducted several quantitative meta-analyses. A pooled analysis of 3 studies found that symptom resolution occurred in 30 of 45 patients (67%) responding to vigabatrin and 40 of 49 patients (82%) responding to ACTH. The difference between groups was statistically significant (odds ratio [OR]: 0.38, 95% confidence interval (CI): 0.15 to 0.99). The authors noted that the limited evidence from RCTs suggests that hormonal treatment (prednisolone, tetracosactide depot and ACTH) resolves infantile spasms faster than vigabatrin and resolves the condition in more children, but long-term developmental and epilepsy outcomes are unknown.

Section summary: There is some evidence from small, generally poor quality RCTs, that ACTH has greater short-term efficacy in resolving infantile spasms than vigabatrin.

Corticosteroid-responsive conditions

The product label for H.P. Acthar gel lists a number of corticosteroid-responsive conditions as indications for repository corticotropin injection, including rheumatoid arthritis, dermatomyositis, symptomatic sarcoidosis, nephrotic syndrome, multiple sclerosis (MS) exacerbations and serum sickness. Evidence that Acthar gel (i.e., ACTH) is a reasonable alternative to corticosteroid treatment requires controlled studies demonstrating superiority or non-inferiority of ACTH to corticosteroids as first-line treatment, or controlled studies showing comparable efficacy of ACTH with fewer adverse effects. Alternatively, for patients unable to tolerate corticosteroids, the most appropriate study design would be a controlled study comparing ACTH to placebo.

The only controlled studies were found for the treatment of MS (i.e., not for other indications). Several RCTs published in the 1960s and early 1970s compared ACTH to placebo for the treatment of acute exacerbations of MS. A study described in recent review articles as the most rigorous of these RCTs was published by Rose and colleagues. (3, 4) This was a multicenter, double-blind study that included 197 patients. Patients were randomized to receive intramuscular injections of ACTH gel or placebo during a 2-week hospitalization for acute exacerbations of MS. The study used Depo-ACTH and placebo, both prepared by the Upjohn Company. Review articles report that the study found that ACTH hastened improvement in symptoms but that the differences between the ACTH and placebo-treated patients was less marked as the dosage of ACTH was reduced during the second week of treatment. (5)

Use of ACTH for treating MS exacerbations decreased in the 1980s as intravenous (IV) corticosteroid treatment became more common. Two RCTs published in the late 1980s compared ACTH to IV corticosteroids. A study by Milanese and colleagues with 30 patients found that

dexamethasone was more effective than ACTH in shortening the length of the exacerbation. (6) Thompson and colleagues published a study that included 61 patients and compared ACTH and high-dose IV methylprednisolone. (7) The authors did not find a statistically significant difference in the efficacy of the 2 treatments. The study was powered to detect a 1-point difference between the 2 groups on Kurtzke's function and disability scales. The scores before and after treatment were not reported.

There are also a limited number of small case series reporting on use of ACTH for other corticosteroid-responsive conditions. For example, in 2011, Bomback and colleagues published a retrospective case series in 21 patients with idiopathic, nondiabetic nephritic syndrome who were treated with ACTH gel. ACTH gel was used as a primary therapy in 3 patients; the other 18 patients had failed a mean of 2.3 immunosuppressive regimens before using ACTH gel. (8) An additional 5 patients were identified who were treated for less than 6 months and were taken off therapy for lack of response; these patients were not included in the analysis. Four of the 21 (19%) patients were in complete remission, defined as stable or improved renal function with final proteinuria falling to less than 500 mg/day. An additional 7 of 21 (33%) patients had a partial remission (at least a 50% reduction in proteinuria and final proteinuria 500 to 3,500 mg/day

Section summary ACTH gel may be considered medically necessary when criteria are met. See policy statements.

Diagnostic testing of adrenocortical function

Diagnostic testing of adrenocortical function is typically done with synthetic ACTH. Studies have evaluated the value of synthetic ACTH for diagnosing adrenal insufficiency. For example, a 2008 meta-analysis identified 13 studies comparing low- and high-dose corticotropin tests for diagnosing adrenal insufficiency. (9) A comparable literature base was not identified for use of H.P. Acthar gel used in the diagnostic testing of adrenocortical function, and no studies were found that compared synthetic ACTH and Acthar gel for this purpose.

Non-corticosteroid-responsive conditions

Repository corticotropin injection has also been proposed for several off-label non-steroid-responsive conditions including tobacco cessation, acute gout, and childhood epilepsy. Controlled studies were identified only for treatment of acute gout. In 2008, Janssens and colleagues published a Cochrane review that examined the efficacy and safety of systemic corticosteroids in the treatment of acute gout in comparison with placebo, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, other active drugs, other therapies including repository corticotropin injection, or no therapy. (10) Three head-to-head trials were identified; 1 of these compared systemic corticosteroids to oral indomethacine and intramuscular ACTH. The quality of the 3 studies identified was graded as very low to moderate. None of the studies found clinically relevant differences between the studied systemic corticosteroids and the comparator

drugs and important safety problems attributable to the used corticosteroids were not reported. The authors concluded that "There is inconclusive evidence for the efficacy and effectiveness of systemic corticosteroids in the treatment of acute gout."

Section summary: There is insufficient evidence from controlled trials that ACTH is a safe and effective treatment of non-corticosteroid-responsive treatments.

Ongoing clinical trials

A search of online site Clinicaltrials.gov database on November 12, 2013 identified 6 ongoing controlled trials evaluating Acthar gel. Four of the ongoing trials are placebo-controlled. Three studies are sponsored by Questcor Pharmaceuticals and, in the other 2 studies, Questcor Pharmacteuticals is a collaborator. The trials are as follows:

Acthar for treatment of proteinuria in diabetic nephropathy patients (NCT01601236): This is a pilot study randomizing patients to 1 of 3 doses of Acthar gel or equivalent volumes of placebo for 36 weeks with a 4-week dose taper. The primary study outcome is percent change in estimated glomerular filtration rate (eGFR) at week 36. The total sample size will be approximately 40 patients and the estimated completion date is June 2014.

Acthar for treatment of proteinuria in membranous nephropathy patients (NCT01386554): The study includes patients with treatment-resistant idiopathic membranous nephropathy. Patients will be randomized to an active treatment or placebo group and will be treated for 24 weeks. The primary outcome is the proportion of patients who have a complete or partial remission in proteinuria at week 28. The total sample size will be approximately 60 patients and the estimated completion date is June 2014.

Acthar for the treatment of systemic lupus erythematosus (SLE) in patients with a history of persistently active disease (NCT01753401): This study includes patients with steroid-dependent, persistently active SLE with arthritic and/or cutaneous involvement. Patients will be randomized to an active treatment or a placebo group. The primary outcome is the proportion of patients who are considered responders at week 4. The total sample size will be approximately 36 patients and the estimated completion date is December 2014.

ACTH in progressive forms of multiple sclerosis (MS) (NCT01950234): The study will compare Acthar gel given to MS patients using a pulsed regimen (i.e. injections on 3 consecutive days per month) and placebo. The primary outcome is the proportion of patients with a 20% worsening in the timed 25-foot walk test (T25FW) at 36 months. The study will include approximately 100 patients and the estimated completion dates is December 2017.

A Phase IV trial of neuroprotection with ACTH in acute optic neuritis (NCT01838174): The study includes patients with a diagnosis of clinically unilateral acute demyelinating optic neuritis and clinical signs and symptoms within the previous 14 days. Patients will be randomized to

receive 15 days of daily injections of Acthar gel or 3 days of intravenous steroid injection followed by 11 days of oral steroid taper. The primary outcome is the average retinal nerve fiber layer (RNFL) thickness at 6 months. The study will include approximately 60 patients and the estimated completion dates is April 2015.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 3 physician specialty societies and 1 academic medical center while this policy was under review for April 2010. In addition, unsolicited input was received from 1 foundation and 3 physicians. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was strong support for use of repository corticotropin in treatment of infantile spasms (West Syndrome).

Summary

While questions still exist about the role of repository corticotropin injection in the treatment of infantile spasms, this has been accepted as a treatment option, and there is strong clinical support for this treatment. Thus, this use may be considered medically necessary.

Practice Guidelines and Position Statements

In 2012, the American Academy of Neurology and the Practice Committee of the Child Neurology Society published an updated evidence-based guideline on treatment of infantile spasms. (11) The guideline included the following recommendations regarding use of ACTH:

- ACTH or vigabatrin may be useful for the short-term treatment of infantile spasms
- ACTH should be preferred over vigabatrin
- Hormonal therapy (ACTH or prednisolone) may be considered for treatment of infants with cryptogenic infantile spasms

In 2012, the American College of Rheumatology published guidelines on therapy and anti-inflammatory prophylaxis of acute gouty arthritis. (12) The guideline committee did not reach a consensus on use of ACTH for patients with acute gout who are able to take medications orally. For patients unable to take oral medications, the committee agreed that subcutaneous synthetic ACTH was a reasonable alternative to oral prednisone or prednisolone therapy.

In 2010, an industry-sponsored Infantile Spasms Working Group published a consensus report on diagnosis and treatment of infantile spasms. (13) Regarding treatment, the report concluded: "At this time, ACTH and VGB (*vigabatrin*) are the only drugs with proven efficacy to suppress clinical spasms and abolish the hyparrhythmic EEG in a randomized clinical trial setting (Mackay et al., 2004) and thus remain first-line treatment."

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

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Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

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Covered when medically necessary:

HCPCS Code	Description
J0800	Injection, corticotropin, up to 40 units

ICD-9-CM Diagnosis Code*	Description
340	Multiple Sclerosis
345.60-345.61	Infantile spasms, code range

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2015:

ICD-10-CM Diagnosis Code*	Description
G35	Multiple sclerosis
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

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES

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1. *H.P. Actar Gel Product Label. Available online at: http://www.acthar.com/pdf/Acthar-PI.pdf. Accessed February 26, 2014.*
2. *Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database Syst Rev 2013; 6:CD001770.*
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4. *Rose AS, Kuzma JW, Kurtzke JF et al. Cooperative study in the evaluation of therapy in multiple sclerosis: ACTH vs placebo in acute exacerbation. Trans Am Neurol Assoc 1969; 94:126-33.*
5. *Berkovich R. Treatment of acute relapses in multiple sclerosis. Neurotherapeutics 2013; 10(1):97- 105.*
6. *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.*
7. *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):969-71.*
8. *Bomback AS, Tumlin JA, Baranski J et al. Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel. Drug Des Devel Ther 2011; 5:147-53.*
9. *Kazlauskaite R, Evans AT, Villabona CV et al. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. J Clin Endocrinol Metab 2008; 93(11):4245-53.*
10. *Janssens HJ, Lucassen PL, Van de Laar FA et al. Systemic corticosteroids for acute gout. Cochrane Database Syst Rev 2008; (2):CD005521.*
11. *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):1974-80.*
12. *Khanna D, Khanna PP, Fitzgerald JD et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken) 2012; 64(10):1447-61.*
13. *Pellock JM, Hrachovy R, Shinnar S et al. Infantile spasms: a U.S. consensus report. Epilepsia 2010; 51(10):2175-89.*

Other sources

Centers for Medicare and Medicaid Services (CMS) Medicare Benefit Policy Manual. Publication 100-02. Chapter 15. Section 50.4.2. Unlabeled Use of Drug. Effective 10/01/03. [Website]: http://www.cms.gov/manuals/Downloads/bp102c15.pdf. Accessed January 6, 2014.

Centers for Medicare and Medicaid Services (CMS) Medicare Benefit Policy Manual. Publication 100-02. Chapter 15. Sections 50, 50.4.1, 50.4.3. Drugs and Biologicals. Effective 10/01/03. [Website]: http://www.cms.gov/manuals/Downloads/bp102c15.pdf. Accessed January 6, 2014.

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X. POLICY HISTORY

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MP 2.162	**CAC 7/26/11** New policy. Adopted BCBSA. Medically necessary for infantile spasms. Not medically necessary as treatment of corticosteroid-responsive conditions, unless there are medical contraindications or intolerance to corticosteroids that are not expected to occur with use of repository corticotropin injection.
	Codes reviewed 12/13/12 klr
	7/24/13 Admin coding review complete--rsb
	CAC 7/30/13 Minor review. References updated. FEP variation revised to refer to the policy manual. Added criteria for treatment of infantile spasms. Added medically necessary indications for treatment of Multiple Sclerosis exacerbations. Policy statements changed to match pharmacy policy. Admin code review complete.
	CAC 3/25/14 Consensus. No changes to policy statements. References updated. Rationale section added.

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