Subject: Acthar Gel (repository corticotropin injection)	**Original Effective Date:** 4/27/2011
Policy Number: MCP-262	**Revision Date(s):** 10/27/2015, Q3 2019
Review Date(s): 10/27/2015; 12/15/2016; 9/19/2017; 7/10/2018; Q3 2020	
MCPC Approval Date: 7/10/2018	
P&T Approval Date: Q3 2019, Q3 2020	

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

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SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Acthar Gel (repository corticotropin injection)** for the treatment of **Infantile spasm (i.e., West Syndrome)** when appropriate criteria are met. There are FDA-approved indications that are listed in the package insert that are not covered by Molina Healthcare since Acthar is not a cost-effective alternative drug that is at least as likely to produce equivalent therapeutic results.

Note: This policy does not apply to cosyntropin (generic Cortrosyn; also referred to as ACTH), which is used for cortisol -stimulation testing.

The intent of the **Acthar Gel (repository corticotropin injection)** policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references and current peer-reviewed scientific literature. The information outlined in the Molina Clinical Policy includes but is not limited to a review of evidence-based information obtained from the following sources Evaluation of New

and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Acthar Gel (repository corticotropin injection)

- A natural form of adrenocorticotropic hormone (ACTH); corticotropin is not a corticosteroid.
- The mechanism of action of repository corticotropin injection in the treatment of infantile spasms is unknown; however, it shares many actions of the corticosteroids due to its ability to increase endogenous corticosteroid synthesis. Repository corticotropin injection and ACTH stimulate the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. Prolonged administration of large doses of repository corticotropin injection induces hyperplasia and hypertrophy of the adrenal cortex and continuous high output of cortisol, corticosterone and weak androgens. The release of endogenous ACTH is influenced by the nervous system via the regulatory hormone released from the hypothalamus and by a negative corticosteroid feedback mechanism. Elevated plasma cortisol suppresses ACTH release. Repository corticotropin injection also binds to melanocortin receptor. Both endogenous ACTH and repository corticotropin injection have a trophic effect on the adrenal cortex which is mediated by cyclic adenosine monophosphate (cyclic AMP).
- Repository corticotropin injection was originally approved by the FDA in 1952 for a broad range of corticosteroid-responsive conditions including rheumatic, collagen, dermatologic, allergic states, ophthalmic, respiratory and edematous states.
- Current labeled indications include multiple sclerosis, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmologic diseases, respiratory diseases, edematous states and infantile spasms in infants and children less than 2 years of age.
- **Although repository corticotropin is FDA approved for other indications and additional inflammatory conditions, there is insufficient evidence for other indications (*including, but not limited to, rheumatic disorders, systemic erythematosus, dermatologic conditions, serum sickness, ophthalmic diseases, and pulmonary sarcoidosis*) that treatment with repository corticotropin results in improved efficacy or safety when compared with other standard treatments.**
- Clinical efficacy and safety data for the majority of indications, with the exception of infantile spasm is lacking. According to the manufacturer little data is available for the general indications of rheumatic, collagen, dermatologic, allergic states, ophthalmic, respiratory, and edematous disorders/diseases and these indications were grandfathered in by the FDA.
    - Common adverse reactions for Acthar Gel are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain (per Acthar prescribing information)
    - 'The differences in the PD outcomes evaluated in this crossover study of healthy subjects are intriguing and support the possibility that the mechanism of action of ACTH analog in inflammatory and autoimmune diseases may differ from that of exogenous corticosteroids. However, extrapolation and relevance of these findings to clinical outcomes in patient populations is unknown and remains to be investigated.' (Lal et al 2016)
    - There is insufficient evidence to conclude that Acthar would be expected to be more effective or better tolerated than intravenous corticosteroids.
- Therefore, while there are additional suggested FDA-labeled uses, statistically robust randomized controlled trials are required to establish the comparative efficacy of Acthar to other available treatments.
- **Due to insufficient evidence to establish efficacy for these indications or superiority to more cost-effective alternatives (such as generic corticosteroids), the use of Acthar HP Gel for any indication**

other than West syndrome will not be authorized. Acthar HP will only be authorized for the treatment of West syndrome (infantile spasms) in pediatric patients under the age of 2 years.

Infantile Spasms (IS)

- The term "infantile spasms" is frequently used synonymously with West syndrome. Infantile spasms, or West syndrome, is a rare disorder that includes a type of epileptic seizure and an electroencephalogram (EEG) finding called hypsarrhythmia. Onset usually occurs before age of one. While the seizures generally resolve by the age of 3, long-term prognosis is poor, with a high incidence of developmental delay, structural neurological abnormalities and persistent seizure activity. IS is characterized by epileptic spasms with onset in infancy or early childhood that are usually associated with the EEG pattern of hypsarrhythmia, and also developmental regression.
- The spasms are sudden, brief contractions of one or more muscle groups, and may be followed by a longer (less than 10 seconds) tonic phase. Most often the spasms, involving the muscles of the neck, trunk and extremities, occur in clusters. The intensity or the frequency of the spasms may increase progressively to a peak, decline, or cease. The clusters tend to occur soon after arousal from sleep.
- The goal of IS treatment is to stop the seizures, normalize the EEG, and optimize the neurodevelopmental outcome.
- Treatment options for IS generally include hormonal therapy, mainly corticotropin (ACTH), and antiseizure medication, mainly vigabatrin. Pyridoxine is often used as first-line therapy for IS in Japan, although there are no randomized controlled trials of this agent as treatment for IS.
    - An FDA committee concluded that there was substantial evidence of effectiveness for Acthar Gel as a treatment for infantile spasms. This conclusion was based upon evidence from 1 randomized controlled trial with confirmatory evidence.
    - The committee agreed that effectiveness has been shown in the cessation of spasms and amelioration of the EEG, however not in the prevention of other seizure types, improvement in long-term developmental outcomes, or any other outcomes.
    - The recommended regimen is a daily dose of 150 U/m^2 (divided into twice-daily intra-muscular injections of 75 U/m2) administered over a 2-week period. Dosing with Acthar Gel should then be gradually tapered over a 2-week period to avoid adrenal insufficiency.
- There remains very low to insufficient evidence for the treatment of IS. Most trials are open label or retrospective analysis. Furthermore, while there is some evidence that supports the effectiveness of ACTH for the short-term treatment of IS and in resolution of hypsarrhythmia, the optimum treatment for IS has yet to be established. The optimal dose and duration of treatment is uncertain. –Refer to 'Background/Summary' section for more information.

Corticosteroid-responsive conditions

- Corticotropin therapy is not curative and generally suppresses the symptoms of chronic diseases without altering the natural course of the disease; it is considered to be supportive therapy to be used adjunctively with other indicated therapies.
- There are a lack of clinical studies comparing the effectiveness of ACTH gel to corticosteroids in corticosteroid-responsive conditions.
    - No randomized clinical studies were found. Only retrospective case series or open-label studies were identified from the literature search. There is no quality evidence of the effectiveness of ACTH gel in those who have failed to respond to corticosteroids.
    - Clinical studies comparing the effectiveness of ACTH gel to corticosteroids in corticosteroid-responsive conditions are limited and has not been shown to be more effective than the use of corticosteroids.

- There is a lack of evidence documenting effectiveness of Acthar HP Gel in patients who have failed to respond to corticosteroids.

- Acthar Gel has limited therapeutic value in those conditions responsive to corticosteroid therapy, in such cases, corticosteroid therapy is considered to be the treatment of choice.
- **Repository corticotropin for corticosteroid-responsive conditions is not a covered because it has not been proven to be more effective than corticosteroids for these indications.**

Diagnostic testing of adrenocortical function

- Corticotropin has been used as a diagnostic aid for detecting adrenocortical insufficiency, however it is not indicated nor the preferred agent for this use.
- An updated label issued in 2010 did not include the use of repository corticotropin injection for diagnostic testing of adrenocortical function, unlike previous versions of the product label.
- Cosyntropin, a synthetic subunit of ACTH, is indicated for this use. Repository corticotropin for diagnostic testing of adrenocortical function has not been shown to be superior to cosyntropin for this purpose.

Multiple Sclerosis

- Acute exacerbations of multiple sclerosis is an FDA-approved indication for repository corticotropin; however the limited studies that compare corticosteroids to ACTH have concluded corticosteroids to be equally safe and effective for the treatment of acute MS exacerbations. Therefore, corticosteroids (such as methylprednisolone and dexamethasone) are more established, cost-effective alternatives and the use of Acthar HP Gel for multiple sclerosis will not be authorized.
- **Published clinical evidence does not demonstrate superiority of Acthar to other available corticosteroids**
- Guidelines from the American Academy of Neurology conclude that glucocorticoid treatment has been demonstrated to have a short-term benefit on the speed of functional recovery in acute attacks of MS. A Type A recommendation was given to consider treatment with glucocorticoids for any patient with an acute attack of MS. (Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the AAN and the MS Council for Clinical Practice Guidelines. Neurology; AAN 2002)
- Additional studies and discussion in the 'Coverage Exclusion' section

FDA INDICATIONS

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

Acthar Gel (repository corticotropin injection) is indicated for the following conditions:

- **Diuresis in nephrotic syndrome:** To induce a diuresis or remission of proteinuria in patients with nephrotic syndrome without uremia of the idiopathic type or due to lupus erythematosus
  Note: Based on the 2012 KDIGO clinical practice guidelines for glomerulonephritis, recommendations cannot be made for the use of corticotropin for initial therapy or relapses of idiopathic membranous nephropathy until more randomized, controlled trials are conducted. The KDIGO guidelines do not include recommendations for use of corticotropin in the treatment of proteinuria due to lupus nephritis.

- **Infantile spasms** Treatment of infantile spasms in infants and children younger than 2 years
  Note: Corticotropin is the preferred treatment in most patients (Child Neurology Society; American Academy of Neurology, 2012)

- **Multiple sclerosis** Treatment of acute exacerbations of multiple sclerosis in adults
  Note: Treatment guidelines recommend the use of high dose IV or oral methylprednisolone for acute exacerbations of multiple sclerosis. Corticotropin may be an alternative therapy if IV corticosteroids cannot be administered or are not tolerated. (AAN; Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2011)

- **Ophthalmic diseases** Treatment of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa (e.g., keratitis, iritis, iridocyclitis, diffuse posterior uveitis, choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation).
  Note: FDA-approved use; however, available data to support use in these conditions are limited.

- **Symptomatic sarcoidosis** Treatment of symptomatic sarcoidosis
  Note: FDA-approved use; however, available data to support use in this condition are limited. Glucocorticoids (e.g., prednisone) are generally recommended as first-line treatment for sarcoidosis (Soto-Gomez N, et al. 2016)

  NOTE: An updated label issued in 2010 did not include the use of repository corticotropin injection for diagnostic testing of adrenocortical function-- unlike previous versions of the product label.

Available as: 5ml vials, 80 units per each ml (400 units per vial)

FDA Approved: 1952**.** Corticotropin received FDA approval in October 2010 for the treatment of infantile spasms in infants and children less than 2 years of age.

Black Box Warnings: *None at the time of this writing*

Prescribing and Access Restrictions

Acthar Gel is only available through specialty pharmacy distribution and not through traditional distribution sources (e.g., wholesalers, retail pharmacies). Hospitals wishing to acquire Acthar Gel should contact CuraScript Specialty Distribution (1-877-599-7748).

After treatment is initiated, discharge or outpatient prescriptions should be submitted to the Acthar Support and Access Program (A.S.A.P.) in order to ensure an uninterrupted supply of the medication. The Acthar Referral/Prescription form is available online at http://www.acthar.com/files/Acthar-Prescription-Referral-Form.pdf.

Additional information is available for the A.S.A.P. at http://www.acthar.com/healthcare-professionals/physician-patient-referrals or by calling 1-888-435-2284.

PHARMACOLOGIC CATEGORY: Hormones and Hormone Modifiers; Adrenal Agents; Corticosteroids; Adrenocorticotropin Stimulating Hormone

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Acthar Gel (repository corticotropin injection) may be authorized for members who meet **ALL** the following criteria **[ALL]**

1. **Prescriber specialty [ONE]**

   - ❒ Prescribed by, or in consultation with, a board-certified pediatric neurologist, pediatric epileptologist, or physician experienced in the management of infantile spasms. Submit consultation notes if applicable.

2. **Diagnosis/Indication [ALL]**
   Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis **[ALL]**

   - ❒ Diagnosis of infantile spasms (IS) confirmed by the presence of hypsarrthymia upon an EEG
     - *The diagnosis of IS in a patient with clinical features is confirmed by electroencephalography (EEG). Most affected patients have an interictal EEG pattern known as hypsarrhythmia (hypsarrthymia is an abnormal chaotic brain wave pattern). In the 2010 consensus report, this EEG pattern was identified as a defining feature of IS. (Pellock JM, et al. Infantile spasms: a U.S. consensus report, 2010; Referenced by Glaze, D in UpToDate: Management and prognosis of infantile spasms. Literature review current through: Jun 2019)*

   - ❒ For individuals with an atypical clinical presentation or lack of hypsarrhythmia on EEG, other causes of spasms have been excluded, including (but not limited to): [AS APPLICABLE]

     - ❍ Epileptic spasms
       - *Spasms can involve the muscles of the neck, trunk, and extremities. Spasms are symmetric contractions of flexor or extensor axial or limb muscles. They vary in pattern, intensity, duration and extent. Most spasms occur in clusters of two to more than 100 over one to several minutes. (Referenced by Glaze, D in UpToDate: Management and prognosis of infantile spasms. Literature review current through: Jun 2019)*

     - ❍ Neuroimaging studies (i.e. CT scan, MRI)
       - *MRI is recommended for all patients with IS. Perform MRI to help determine etiology of spasms. Approximately 70 percent of patients will have an established etiology after clinical evaluation, EEG, and MRI. Neuroimaging studies should be performed in all patients with IS to identify lesions associated with the disorder, as this may influence treatment decisions.*

3. Age/Gender/Other restrictions [ALL]

- ❒ Less than 2 years of age [< 24 months]
  - *Indicated as monotherapy for the treatment of infantile spasms in children under 2 years of age*

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ For use as **monotherapy** in the treatment of infantile spasms
  - *Indicated as monotherapy for the treatment of infantile spasms in children under 2 years of age*

- ❒ Member does not have a suspected congenital infection [i.e. Cytomegalovirus (CMV), Hepatitis, Herpes, Rubella, Syphilis, Toxoplasmosis]. Documentation required.
  - *Contraindicated in children under 2 years of age with suspected congenital infections.*

- ❒ Treatment plan submitted by Prescriber includes the following: [ALL]
  - ❍ Daily dosages in IU
  - ❍ Member's surface area in m^2
  - ❍ Expected treatment course including dose tapering protocols
  - ❍ Repository corticotropin injection dosing for infantile spasm is prescribed as follows: [ALL]
    - Initial dose: 75 U/m^2 intramuscular (IM) twice daily for 2 weeks
    - After 2 weeks, dose should be tapered according to the following schedule: 30 U/m^2 IM in the morning for 3 days; 15 U/m^2 IM in the morning for 3 days; 10 U/m^2 IM in the morning for 3 days; and 10 U/m^2 IM every other morning for 6 days (3 doses)

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Intravenous administration
- ❒ Concomitant use of live or live attenuated vaccines when receiving immunosuppressive corticotropin dose
- ❒ Congenital infection in infants
- ❒ Congestive heart failure
- ❒ Hypertension, uncontrolled
- ❒ Intravenous administration
- ❒ Ocular herpes simplex infection
- ❒ Osteoporosis
- ❒ Peptic ulcers, history or presence of
- ❒ Primary adrenocortical insufficiency or adrenocortical hyperactivity
- ❒ Scleroderma
- ❒ Sensitivity to porcine protein
- ❒ Surgery, recent
- ❒ Systemic fungal infection

Exclusions

There is insufficient evidence demonstrating the safety and efficacy of Acthar for the use in the conditions listed below. FDA-approved indications may not be covered by Molina Healthcare if it is determined based on review of available evidence that Acthar is not a cost-effective treatment that is at least as likely to produce equivalent therapeutic results to other established or alternative treatments available. Therefore the following conditions will NOT be authorized: [ANY]

- ❑ Multiple sclerosis: acute exacerbation
- ❑ Edematous state: nephrotic syndrome
- ❑ Rheumatic disorders: psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis
- ❑ Collagen diseases: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)
- ❑ Dermatologic diseases: severe erythema multiforme, Stevens- Johnson syndrome
- ❑ Allergic states: serum sickness
- ❑ Ophthalmic diseases: keratitis iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation
- ❑ Respiratory diseases: symptomatic sarcoidosis

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

REAUTHORIZATION /CONTINUATION OF THERAPY

Continuation of Therapy is an **EXCEPTION** determined appropriate by the **Medical Director**. The clinical studies cited in the FDA labeling and manufacturer's package insert is limited to 2 weeks of treatment with gradual tapering of the dosage over a 2-week period.

Continuation of therapy past 4 weeks (as indicated in the FDA labeling and manufacturer's package insert) is an EXCEPTION and will **not** be authorized unless **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❒ Member currently meets ALL initial coverage criteria

- ❒ Prescribed by, or in consultation with, a board-certified pediatric neurologist, pediatric epileptologist, or physician experienced in the management of infantile spasms.

2. Compliance

- ❒ Medical Director Review required

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ Member has experienced substantial clinical benefit from therapy. Documentation required.
  - *According to the FDA medical reviewer of the pivotal trials for infantile spasm, the combined endpoint of elimination of spasms and hypsarrhythmia is generally recognized as the most clinically meaningful endpoint for efficacy studies of infantile spasms.*

- ❒ Submission of progress notes with taper schedule intended if continuation of treatment is authorized
  - *The consensus of experts in a 2010 review was that effective treatment of IS defined by complete cessation of spasms and resolution of hypsarrhythmia on electroencephalography (EEG).*
  - *A standard EEG to evaluate interictal activity may miss the hypsarrhythmia pattern, which can be variably present in an awake child, but is detected more sensitively in sleep. As a result, video-EEG monitoring is ideally used to assess treatment response in children with IS.*

- ❒ Additional documentation or peer-to-peer may be required at the discretion of the Medical Director

4. Exclusion and Discontinuation of Treatment [ANY]

Exclusion to, and discontinuation of, treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: GI bleeding; gastric ulcer; hypertension; hypokalemia; severe depression; frank psychotic manifestations; posterior subcapsular cataracts; glaucoma
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
  - ❍ Non-FDA approved indications
  - ❍ Intravenous administration
  - ❍ Concomitant use of live or live attenuated vaccines when receiving immunosuppressive corticotropin dose (has received or will receive a live or live attenuated vaccine within 6 weeks of intended Acthar Gel administration)
  - ❍ Congenital infection in infants
  - ❍ Congestive heart failure
  - ❍ Hypertension, uncontrolled
  - ❍ Intravenous administration
  - ❍ Ocular herpes simplex infection
  - ❍ Osteoporosis
  - ❍ Peptic ulcers, history or presence of
  - ❍ Primary adrenocortical insufficiency or adrenocortical hyperactivity
  - ❍ Scleroderma
  - ❍ Sensitivity to porcine protein
  - ❍ Surgery, recent
  - ❍ Systemic fungal infection

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

Infantile Spasms

- ❑ Older than 2 years: Not indicated in this population

- ❑ Younger than 2 years:
  - ❍ Usual dosage: 75 units/m^2/dose IM twice daily for 2 weeks
  - ❍ After 2 weeks, dose should be tapered according to the following schedule: 30 U/m^2 IM in the morning for 3 days; 15 U/m^2 IM in the morning for 3 days; 10 U/m^2 IM in the morning for 3 days; and 10 U/m^2 IM every other morning for 6 days (3 doses)

- ◆ The optimal dose of ACTH is not known and may differ in individual patients. One approach is to initiate ACTH 20 to 30 units/day IM (dose not adjusted for body weight). After re-evaluation in two weeks may increase to 40 units/day if spasms or hypsarrhythmia persist. An alternative approach using a high-dose regimen has been proposed. It consists of treatment with ACTH in a dose of 75 units/m^2 twice daily IM for two weeks. The dose then is tapered as 30, 15, and 10 units/m2 each morning for three days each, then 10 U/m2 every other morning for six days.
- ◆ According to a report of the American Academy of Neurology and the Child Neurology Society (2004) on the treatment of IS, ACTH is effective for the short-term treatment of IS and the resolution of hypsarrhythmia; however, there is insufficient evidence to recommend optimum dosage and duration of treatment. Therefore, provisions for exceptional cases to extend Acthar therapy, must be upon a request from pediatric epilepsy specialist and forward to a Molina Medical Director for review.
- ◆ The labeling of H.P Acthar gel states that, although drug dependence does not occur, sudden withdrawal of repository corticotropin gel after prolonged use may lead to adrenal insufficiency or recurrent symptoms which make it difficult to stop the treatment. It may be necessary to taper the dose and increase the injection interval to gradually discontinue the medication.
- ◆ Body surface area calculation: BSA (m^2) = the square root of ([height (cm) x weight (kg)] / 3600)

2. Authorization Limit [ALL]

- ❒ Quantity limit: Authorization will be based on FDA-approved dosing guidelines and will take into consideration the duration of the treatment period as well as the taper period that is requested by the treating physician.
  - ❍ Infantile spasms: 150 units/m^2/day (75 U/m^2 twice daily)
  - ❍ Dispensing limit: ONE (1) 5mL vial for infantile spasms

- ❒ Duration of initial authorization
  - ❍ Infantile spasms
    One course of therapy; 4 weeks (2 weeks of treatment, and 2 weeks of taper). **EXCEPTIONS:** Coverage beyond 4 weeks of therapy is an exception determined appropriate by the Medical Director.

- *The 2010 consensus statement suggests initiating a taper of ACTH after two weeks of therapy at the maximum dose (Pellock JM, et al. Infantile spasms: a U.S. consensus report, 2010; Referenced by Glaze, D in UpToDate: Management and prognosis of infantile spasms. Literature review current through: Jun 2019)*

❒ Continuation of treatment: Coverage beyond 1 month as indicated in the labeling (2 week treatment + 2 week recommended taper) is an **EXCEPTION** determined appropriate by the **Medical Director**. The clinical studies cited in the FDA labeling and manufacturer's package insert is limited to 2 weeks of treatment with gradual tapering of the dosage over a 2-week period.

❒ Duration of continuation of treatment: May be authorized up to **one course** (2 week treatment + 2 week recommended taper) of therapy at a time
- *Relapses are not uncommon among patients who responded to an initial treatment course. No data is available to guide therapy in these cases. Typically, a second course (four to six weeks) of the agent that was previously effective in obtaining control is administered (Pellock JM, et al. Infantile spasms: a U.S. consensus report, 2010; Referenced by Glaze, D in UpToDate: Management and prognosis of infantile spasms Literature review current through: Jun 2019).*

3. Route of Administration [ALL]

❒ Acthar Gel (repository corticotropin injection) is administered intramuscularly (should never be given intravenously). May be self-administered or provider-administered.

❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

❑ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

COVERAGE EXCLUSIONS

All other uses of Acthar Gel (repository corticotropin injection) that are not an FDA-approved indication or FDA-approved indications that are not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

UNSUPPORTED USES

Acthar gel was approved by the U.S. FDA in 1952, prior to the implementation of 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. There is insufficient evidence demonstrating the safety and efficacy of Acthar for the use in the conditions listed below. FDA-approved indications may not be covered by Molina Healthcare if it is determined based on review of available evidence that Acthar is not a cost-effective treatment that is at least as likely to produce equivalent therapeutic results to other established or alternative treatments available. Therefore the following conditions will NOT be authorized

- **Multiple sclerosis: acute exacerbation**
  - According to the product label, "Controlled clinical trials have shown H.P Acthar Gel to be effective in speeding resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease."
  - Treatment with glucocorticoids for patients with an acute MS exacerbation that results in neurologic symptoms and increased disability or impairments in vision, strength, or cerebellar function is recommended (Olek, MJ and Howard J. 2019). **The preferred regimen is intravenous methylprednisolone 1000 mg daily for five days without an oral taper.**
  - A head-to-head clinical trial compared a 14-day course of intravenous methylprednisolone to intramuscular ACTH gel in the treatment of acute relapse in 61 patients with multiple sclerosis (Thompson AJ, et al. 1989). Subjects randomized to methylprednisolone received 1 gram IV methylprednisolone daily for 3 days and 14 days of intramuscular placebo, and subjects randomized to ACTH gel received IV placebo daily for 3 days and at the same time a reducing course of intramuscular ACTH over 14 days, consisting of 80 units for 7 days, 40 units for 4 days, and 20 units for 3 days.

    At the end of twelve weeks, there was no statistically significant difference between the two regimens in the symptoms of multiple sclerosis as measured by the expanded disability symptom scale (EDSS or Kurtzke status scale). The authors reported that there was a marked improvement in both groups over the course of the study, but no differences between groups in either the rate of recovery or final outcome in acute relapse. The authors noted that side effects in the methylprednisolone group were less frequent than in the ACTH group. The authors stated that giving a 3-day course of intravenous treatment rather than 14 days of intramuscular injections "has obvious advantages in terms of both patient comfort and medical resources."
  - In 2013, an update to the 2000 Cochrane review was published evaluating efficacy and safety of corticosteroids or adrenocorticotropic hormone (ACTH) in reducing short and long-term morbidity associated with multiple sclerosis (MS) [Filippini G, Cochrane Database Syst Rev 2000]
    - A systematic review and meta-analysis published in 2000 identified six randomized controlled trials comparing methylprednisolone or ACTH with placebo in a total of 377 patients with acute exacerbations of MS (Filippini G, 2000). Methylprednisolone was tested in four trials with 140 patients; it was administered orally in one trial (500 mg daily for five days followed by a 10 day taper), and intravenously in three trials (500 mg daily or 1000 mg daily for five

days in two trials, and 15 mg/kg daily for three days in the third). The following observations were reported:
    - Compared with placebo, patients treated with ACTH or methylprednisolone had a significant reduction in the risk of either worsening or not improving within five weeks from randomization (odds ratio [OR] 0.37, 95% CI 0.24-0.57).
    - In a subgroup analysis by drug, both methylprednisolone treatment and ACTH treatment reduced the risk of worsening or not improving within five weeks.
- The trials evaluated showed that corticosteroids (methylprednisolone or ACTH favored recovery from acute exacerbation in MS, which increased the probability of ameliorating the episode within the first five weeks of treatment by more than 60%. Evidence found that corticosteroids, notably methylprednisolone, are effective in the treatment of acute exacerbation, increasing the probability of ameliorating the episode and speeding up patient recovery.
- There was insufficient evidence to determine if steroids or ACTH treatment prevented new exacerbations and worsening of long term disability in MS.
- **Evidence on the efficacy of different types or schedules of therapies was limited. Indirect comparisons suggest a significantly greater effect of MP versus ACTH.**

◆ National Institute for Health and Care Excellences (NICE)
A NICE Clinical Guideline from 'Management of Multiple Sclerosis (MS) in Primary and Secondary Care,' noted some evidence for steroid use comes from older trials that had used ACTH, however ACTH is no longer used as a treatment option for acute relapse of MS. The Guideline Development Group (GDG) considered that steroids are generally the standard accepted treatment for relapse and that delivery is dependent on service organization.

❑ **Corticosteroid-responsive conditions**

❑ **Edematous state: nephrotic syndrome**

❑ **Rheumatic disorders: psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis**

◆ Psoriatic arthritis: Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of rheumatic disorders, including adjunctive therapy for acute episodes/exacerbations of psoriatic arthritis, there is insufficient evidence to recommend the use of corticotropin for this indication. Clinical guidelines do not include recommendations for use of corticotropin in rheumatic disorders (Singh JA, et al. 2018 ACR)

◆ Rheumatoid arthritis: Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of rheumatic disorders, including rheumatoid arthritis (including juvenile idiopathic arthritis and/or ankylosing spondylitis), there is insufficient evidence to recommend the use of corticotropin for this indication. Clinical guidelines do not include recommendations for use of corticotropin in rheumatic disorders (Singh JA, et al. 2015 ACR)

❑ **Collagen diseases: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)**

◆ **Dermatomyositis:** Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of collagen diseases, including dermatomyositis polymyositis, there is insufficient evidence to recommend the use of corticotropin for this indication. Clinical guidelines do not include recommendations for use of corticotropin in collagen diseases (Miller M. 2019)

- **Systemic lupus erythematosus:** Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of collagen diseases, including systemic lupus erythematosus, there is insufficient evidence to recommend the use of corticotropin for this indication. Clinical guidelines do not include recommendations for use of corticotropin in collagen diseases.

- ❑ **Dermatologic diseases**
  - **Erythema multiforme:** Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of dermatologic diseases, including severe erythema multiforme, there is insufficient evidence to recommend the use of corticotropin for this indication (Wetter D. 2019)
  - **Stevens-Johnson syndrome:** Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of dermatologic diseases, including Stevens-Johnson syndrome, there is insufficient evidence to recommend the use of corticotropin for this indication. [Reference: 1) Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. 2010; 2) High W. 2019]

- ❑ **Allergic states**
  - **Serum sickness** Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of serum sickness, there is insufficient evidence to recommend the use of corticotropin for this indication. [Reference: 1) Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. 2010; 2) Wener M. 2019]

- ❑ **Ophthalmic diseases: keratitis iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation**

- ❑ **Respiratory diseases: symptomatic sarcoidosis**

- ❑ **Diagnostic testing of adrenocortical function**
  The drug is no longer indicated for diagnostic testing of adrenocortical function. An updated label issued in 2010 did not include the use of repository corticotropin injection for diagnostic testing of adrenocortical function, unlike previous versions of the product label. Cosyntropin, a synthetic subunit of ACTH, is approved for this use. Repository corticotropin for diagnostic testing of adrenocortical function has not been shown to be superior to cosyntropin for this purpose.

- ❑ **Primary adrenocortical insufficiency or congenital adrenogenital syndrome**

BACKGROUND/SUMMARY

Infantile Spasms (i.e., West Syndrome)

- Evidence remains very low to insufficient for the treatment of infantile spasms (IS). Most trials are open-label or retrospective analysis.

- FDA approval of ACTH for the treatment of IS was based on *one pivotal* and *one supportive clinical trial.* Unlike the conventional process for drug approvals, in which pivotal studies are submitted to the FDA for approval, Questcor Pharmaceuticals re-analyzed data from the previously published studies; there was no prospectively defined statistical analysis. In both clinical trials, patients were evaluated by electroencephalogram (EEG) before initiation of treatment (to confirm the presence of clinical spasms and the EEG pattern) and after the end of the treatment period to evaluate response to therapy. The primary outcome, overall response, defined as complete cessation of spasms and resolution of the EEG pattern on video EEG, is a widely accepted definition of clinical success in the expert community (*Advisory Committee Briefing Document NDA 22-432*).

- Corticotropin injection received FDA approval for infantile spasms in 2010 based on a 1996 single blinded clinical trial comparing a 2 week course of ACTH 75 u/m^2 twice daily to prednisone 1 mg /kg twice daily in 29 infants under 2 years of age (n=29) (Baram TZ, et al. 1996).
  - Baram et al. published a pivotal, single-blind study comparing high-dose ACTH administered as 75 Units/m^2 IM BID (150 mg Units QD) and prednisone 2 mg/kg/day given as 1 mg/kg PO BID. Infants with clinical IS and no previous steroid or ACTH treatment were randomized to receive ACTH (n = 15) or prednisone (n = 14) for 2 weeks with a gradual taper to zero for an additional 2 weeks. Patients with persistent spasms or hypsarrhythmia after initial treatment were offered the alternative treatment.
  - The treating physician was not blinded to treatment assignment, but the EEGs were read by a blinded evaluator. The median age was slightly higher in the prednisone group compared to the ACTH group. The primary outcome was the number in each group who were treatment responders, defined as having a complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG. After treatment, 13 (86.7%) of those randomized to ACTH compared to 4 (28.6%) of those given prednisone responded (p=0.0015). The lack of double blinding and small nature of this study add risk of bias to the results and should be interpreted with caution. In addition, there was not a defined statistical plan and the primary outcomes were not chosen in advance by authors.
  - The Questcor analysis of the efficacy data demonstrated that the combined clinical endpoint of spasm cessation and resolution of hypsarrhythmic EEG favored ACTH (13/15, 86.7%) compared to prednisone (4/14, 28.6%) ($p < 0.002$). The difference between ACTH and prednisone was significant for both EEG response (86.7% vs. 28.6%, $p = 0.0015$) and spasm cessation (93.3% vs. 28.6%, $p = 0.0003$). For patients who did not respond to the original treatment and were crossed-over to alternative therapy, results showed that 1 of 2 patients who failed ACTH responded to prednisone and 7 of 8 patients (87.5%) who did not respond to prednisone responded to ACTH.
  - Even though this pivotal study showed that ACTH was superior to prednisone in IS, the lack of pre-specified statistical analysis and the limited power to detect a difference in response rates in the re-analysis are limitations.

- The supportive efficacy study was a prospective, randomized, controlled, single-blind trial (Hrachovy RA, et al. 1994).
  Patients were randomized to treatment with once-a-day low-dose (LD) ACTH (20 Units IM QD, n = 29) for a short-duration (2 weeks treatment followed by a 2 weeks taper in responders or a dose escalation to 30 Units/d in non-responders) or once-a-day high-dose (HD) ACTH (150 Units/m2QD n = 30) for a long-duration (3 weeks treatment followed by a 9 week taper). Even though 59 patients were enrolled in the study, 9 of them did not complete the treatment protocol, which had a considerable impact on the results of the study. Information was recovered for 8 of these patients. In the intent-to-treat (ITT) population, which included all 59 randomized patients, there was no significant difference between the HD and LD groups in overall response (50% vs. 52%, p = 0.94) or either of the 2 secondary endpoints: spasm control alone (77% vs. 55%, p = 0.07) or EEG response alone (53% vs. 62%, p = 0.52). An independent analysis by the sponsor was based on a modified intent-to-treat (mITT) population (n = 51), which included all patients who received at least one dose of drug and had adequate data for evaluation. The overall response rate (62.5% vs. 48.1%, p = 0.2768) was also non-significant, which was attributed to the once-daily administration of ACTH in this trial. Analysis of the secondary efficacy results in the mITT population did not establish significance for the hypsarrhythmic EEG pattern response rate, but demonstrated a greater spasm control response rate in the HD group (79.2%, 19/24) than in the LD group (51.9%, 14/27) with nominal statistical significance (p = 0.0329).

- **Adverse Reactions** Common adverse reactions for repository corticotropin are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain. Specific adverse reactions resulting from use of repository corticotropin in children less than 2 years of age are increased risk of infections, hypertension, irritability, Cushingoid symptoms, cardiac hypertrophy and weight gain. Serious adverse events associated with repository corticotropin are also similar to those of corticosteroids and include increase susceptibility to infections, adrenal suppression after prolonged use, Cushing's syndrome, gastrointestinal perforation and bleeding, and negative effects on growth and development.

CONSENSUS GUIDELINES AND EVIDENCE-BASED REVIEWS

Treatment of IS has been evaluated in several consensus guidelines and evidence-based reviews, including a 2004 American Academy of Neurology (AAN) and Child Neurology Society (CNS) (Mackay et al, 2004) and an updated 2012 practice parameter (Go et.al, 2012); a 2013 Cochrane systemic review (Hancock, et.al 2013); and a 2010 United States consensus report (Pellock, et.al. 2010).

- Conclusions were limited by the overall poor methodology of the available studies
- Lack of adherence to standardized case definitions and outcome measures is one problem with many studies. Another is that inclusion of a control group is critical, as the natural history of the disease is that clinical spasms subside and electroencephalogram patterns evolve without therapy, yet many clinicians would be reluctant not to treat as there is some observational data that delayed therapy may worsen prognosis.
- Therefore, the mechanism, optimal drug, dose, duration of therapy, and the importance of prompt initiation of treatment after the appearance of spasms still remain to be determined.

- American Academy of Neurology (AAN) and Child Neurology Society (CNS)

  The 2004 AAN/CNS practice parameter on treatment of infantile spasms in children was updated in 2012 (Mackay et al, 2004) (Go et.al, 2012).

  The recommendations of the AAN/CNS regarding medical treatment of IS in children is as follows for adrenocorticotropic hormone (ACTH):

  - The evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as ACTH for short-term treatment of infantile spasms (Level U).
  - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B)
  - ACTH (Level B) or VGB (Level C) may be offered for short-term treatment of infantile spasms. Evidence suggests that ACTH may be offered over VGB (Level C).
  - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome (Level C).
  - A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB may be considered to improve long-term cognitive outcomes (Level C).

  AAN Rating of Recommendation:

  - *Level A: Established as effective, ineffective or harmful for the given condition in the specified population*
  - *Level B: Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population.*
  - *Level C: Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population.*
  - *Level U: Data inadequate or conflicting. Given current knowledge, treatment is unproven.*

- International League against Epilepsy (ILAE) Epilepsy Guidelines Task Force (2015)
  - A Task Force of the Commission of Pediatrics developed a consensus document addressing diagnostic markers, management interventions, and outcome measures for infants with seizures in 2015 (Wilmshurst, et al. 2015). Levels of evidence to support recommendations and statements were assessed using the American Academy of Neurology Guidelines and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
  - According to the Task Force, 'There is no high level evidence to support any particular current agents for use in infants with seizures. Adrenocorticotropic hormone (ACTH) is preferred for short-term control of epileptic spasms (level B recommendation), oral steroids are probably effective in short-term control of spasms (level C recommendation), and a shorter interval from the onset of spasms to treatment initiation may improve long-term neurodevelopmental outcome (level C recommendation).'

DEFINITIONS

N/A

APPENDIX

N/A

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP TO DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description

HCPCS	Description
J0800	Injection, corticotropin, up to 40 units *Acthar Gel is supplied in 5ml vials, 80 units per each ml (400 units per vial)*

*CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

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Policy History	Approval
Policy Developed Peer Review. AMR Tracking Num: 236128. 1/27/2011. Board certified in Internal Medicine, Endocrinology, Diabetes and Metabolism. Peer Review. AMR Tracking Num: 236134. 1/27/2011. Board certified in Neurology Peer Review. AMR Tracking Num: 236136. 1/28/2011. Board certified in Internal Medicine, Rheumatology	4/27/2011
Revision Peer Review. AMR Tracking Num: 614710. 10/2/2015. Board certified in Pediatrics, Pediatric Hematology/Oncology.	10/27/2015
Revision Peer Review: AMR Peer Review Network. 7/29/2019. Practicing Physician. Board certified in Neurology	P&T Q3 2019
Annual Review* No coverage criteria changes with this annual review. Minor revisions, including clarification and addition of language, however no change to intent	P&T Q3 2020

*NOTE: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.