Original Effective Date: 04/27/2011
Current Effective Date: 11/23/2023
Last P&T Approval/Version: 10/25/2023
Next Review Due By: 10/2024
Policy Number: C8373-A

Acthar Gel (repository corticotropin injection)

PRODUCTS AFFECTED

Acthar Gel (repository corticotropin injection), Cortrophin Gel (repository corticotropin injection)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Infantile spasm (IS)

REQUIRED MEDICAL INFORMATION:
This policy addresses the coverage of 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 repository corticotropin injection is not a cost-effective alternative drug that is at least as likely to produce equivalent therapeutic results.
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. (See Appendix for further details)
Due to insufficient evidence to establish efficacy for these indications or superiority to more cost-effective alternatives (such as generic corticosteroids), the use of repository corticotropin for any indication other than West syndrome will not be authorized. Repository corticotropin will only be authorized for the treatment of West syndrome (infantile spasms) in pediatric patients under the age of 2 years.

A. INFANTILE SPASMS (IS):

1. (a) Documentation of diagnosis of infantile spasms (IS) confirmed by the presence of hypsarrhythmia upon an EEG [DOCUMENTATION REQUIRED]
   OR
   (b) Documentation (for members with an atypical clinical presentation or lack of hypsarrhythmia on EEG) other causes of spasms have been excluded, including (but not limited to) epileptic spasms on neuroimaging studies (i.e., CT scan, MRI) [DOCUMENTATION REQUIRED]:
   AND
2. Prescriber attests that repository corticotropin injection will be used as monotherapy in the treatment of infantile spasms
   AND
3. Prescriber attests that member does not have a suspected congenital infection [i.e., Cytomegalovirus (CMV), Hepatitis, Herpes, Rubella, Syphilis, Toxoplasmosis]
   AND
4. Documentation of a treatment plan submitted by Prescriber that includes ALL of the following:
   a) Daily prescribed dose
   b) Member's body surface area (BSA) in m^2
   c) Expected treatment course including dose tapering protocols
   AND
5. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]
   AND
6. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to repository corticotropin injection include: intravenous administration; infants under 2 years of age who have suspected congenital infections; concomitant administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of repository corticotropin, patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction, or sensitivity to proteins of porcine origin]

B. NON-COVERAGE OF UNSUPPORTED USES:

1. See APPENDIX for unsupported uses
   Corticotropin 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 corticotropin 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 corticotropin 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:
   (a) Multiple Sclerosis
   (b) Corticosteroid-Responsive Conditions
   (c) Edematous State: Nephrotic Syndrome
   (d) Rheumatic Disorders: Psoriatic Arthritis, Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Ankylosing Spondylitis
   (e) Collagen Diseases: Systemic Lupus Erythematosus, Systemic Dermatomyositis
   (f) Dermatologic Diseases
   (g) Allergic States
   (h) Ophthalmic Diseases: Keratitis Iritis, Iridocyclitis, Diffuse Posterior Uveitis and Choroiditis, Optic Neuritis, Chorioretinitis, Anterior Segment Inflammation
   (i) Respiratory Diseases: Symptomatic Sarcoidosis

(j) Diagnostic Testing of Adrenocortical Function
(k) Primary Adrenocortical Insufficiency or Congenital Adrenogenital Syndrome

CONTINUATION OF THERAPY:

A. INFANTILE SPASMS (IS):

Continuation of Therapy is an EXCEPTION determined appropriate by the Medical Director/Clinical Pharmacist. 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:

1. Documentation that member has experienced substantial clinical benefit from therapy [DOCUMENTATION REQUIRED]
   AND
2. Submission of progress notes with treatment plan (i.e., daily prescribed dose and member BSA in m2) and taper schedule intended if continuation of treatment is authorized. Additional documentation or peer-to-peer may be required at the discretion of the Medical Director/Clinical Pharmacist. [DOCUMENTATION REQUIRED]

DURATION OF APPROVAL:

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/Clinical Pharmacist. Duration of continuation of treatment: May be authorized up to one course (2-week treatment + 2-week recommended taper) of therapy at a time.

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified pediatric neurologist, pediatric epileptologist, or physician experienced in the management of infantile spasms. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

Less than 2 years of age

QUANTITY:

Infantile spasms: 150 units/m^2/day (75 U/m^2 twice daily) for 2 weeks.
After 2 weeks, dose should be tapered according to the following schedule: 30 units/m2/dose every morning for 3 days, 15 units/m2/dose every morning for 3 days, 10 units/m2/dose every morning for 3 days, and 10 units/m2/dose every other morning for 6 days.
Dispensing limit: One course of therapy

PLACE OF ADMINISTRATION:

The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the intramuscular injectable products administered in a place of service that is a non-hospital facility- based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Intramuscular

DRUG CLASS:

Corticotropin

FDA-APPROVED USES:

ACTHAR GEL (repository corticotropin injection) is indicated for:

- Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.
- The treatment of exacerbations of multiple sclerosis in adults.

Acthar Gel may be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state.

COMPENDIAL APPROVED OFF-LABELED USES:
None (See Also- CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION)

APPENDIX

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 corticotropin 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 corticotropin 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

APPENDIX:
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 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 (per corticotropin 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 corticotropin 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 corticotropin 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 corticotropin for any indication other than West syndrome will not be authorized. corticotropin will only be authorized for the treatment of West syndrome (infantile spasms) in pediatric patients under the age of 2 years.

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 corticotropin in patients who have failed to respond to corticosteroids.
- Corticotropin 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 corticotropin for multiple sclerosis will not be authorized.
- Published clinical evidence does not demonstrate superiority of corticotropin 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

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

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.

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.

<u>American Academy of Neurology (AAN) and Child Neurology Society (CNS)</u>

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).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of repository corticotropin injection 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. Contraindications to repository corticotropin injection include: intravenous administration; infants under 2 years of age who have suspected congenital infections; concomitant administration of live or live attenuated vaccines in patients receiving immunosuppressive doses; patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction, or sensitivity to proteins of porcine origin.

OTHER SPECIAL CONSIDERATIONS:

None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J0801	Injection, corticotropin (acthar gel), up to 40 units
J0802	Injection, corticotropin (ani), up to 40 units

AVAILABLE DOSAGE FORMS:

Acthar GEL 80UNIT/ML
Cortrophin GEL 80UNIT/ML

REFERENCES

1. Acthar Gel (repository corticotropin injection) [prescribing information]. Bedminster, NJ: Mallinckrodt ARD Inc; October 2021.
2. Purified Corticotrophin gel (repository corticotropin injection) [prescribing information]. Baudette, MN: ANI Pharmaceuticals; November 2021.
3. U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Acthar Gel(NDA 22-432). Background Package. Peripheral and Central Nervous System Drugs Advisory Committee Meeting. Silver Spring, MD: FDA; May 6, 2010.
4. U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting. Silver Spring,MD: FDA; May 6, 2010.
5. Baram TZ, Mitchell WG, Tournay A, et al. High-dose corticotropin (ACTH) versus prednisone for infantiles pasms: a prospective, randomized, blinded study. Pediatrics 1996;97:375-379.
6. 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.
7. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database Syst Rev 2013; CD001770.
8. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia 2010; 51:2175.
9. 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 Aug;56(8):1185-97.
10. Bertsias G, Ioannidis JP, Boletis J, et al; Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis*. 2008;67(2):195-205.[PubMed 17504841]10.1136/ard.2007.070367
11. Mackay MT, Weiss SK, Adams-Webber T, et al. American Academy of Neurology; Child Neurology Society.Practice parameter: Medical treatment of infantile spasms: Report of the American Academy of Neurology and the Child Neurology Society. Neurology. 2004;62(10):1668-1681.
12. Go CY, Mackay MT, Weiss SK, et al; Child Neurology Society; American Academy of Neurology. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2012;78(24):1974-1980.[PubMed 22689735] Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3369510/

Multiple Sclerosis

1. Berkovich, Regina Radner. Acute Multiple Sclerosis Relapse. CONTINUUM: Lifelong Learning in Neurology 22.3, Multiple Sclerosis and Other Demyelinating Diseases (2016): 799-814.
2. Filippini G, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD001331. DOI: 10.1002/14651858.CD001331. Last updated April 20, 2013.
3. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database Syst Rev. 2013; (6):CD001770.
4. 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. PubMed PMID: 2544829.
5. Burton JM, O'Connor PW, Hohol M, Beyene J. Oral versus Intravenous Steroids for Treatment of Relapses in Multiple Sclerosis. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD006921. DOI: 10.1002/14651858.CD006921.pub2.

6. National Institute for Health and Care Excellence (NICE). Multiple sclerosis in adults: management. NICE clinical guideline CG186. London, UK: National Institute for Health and Care Excellence; October 2014. nice.org.uk/guidance/cg186.
7. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology. 2002;58(2):169–178.
8. Scott TF, Frohman EM, De Seze J, et al.; Therapeutics and Technology Assessment Subcommittee of American Academy of Neurology. 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;77(24):2128-2134.[PubMed 22156988]
9. 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.
10. 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):969-971.

Other conditions

1. Lal, Ritu, et al. Pharmacodynamics and tolerability of repository corticotropin injection in healthy human subjects: A comparison with intravenous methylprednisolone. The Journal of Clinical Pharmacology 56.2 (2016): 195-202.
2. Soto-Gomez N, Peters JI, Nambiar AM. Diagnosis, and management of sarcoidosis. Am Fam Physician. 2016;93(10):840-848. [PubMed 27175719]
3. Singh JA, Guyatt G, Ogdie A, et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Rheumatol*. 2019;71(1):5-32.[PubMed 30499246]10.1002/art.40726
4. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68(1):1-26. [PubMed 26545940]10.1002/art.39480
5. 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. *Ann Allergy Asthma Immunol*. 2010;105(4):259-273.[PubMed 20934625]10.1016/j.anai.2010.08.002
6. Scott TF, Frohman EM, De Seze J, et al.; Therapeutics and Technology Assessment Subcommittee of American Academy of Neurology. 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;77(24):2128- 2134.[PubMed 22156988]

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Place of Administration Coding/Billing Information	Q4 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Quantity Appendix Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file