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Medication Policy Manual **Policy No:** dru316

Topic: repository corticotropin **Date of Origin:** July 12, 2013

- Acthar Gel
- Purified Cortrophin Gel

Committee Approval Date: December 7, 2022 **Next Review Date:** 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is a medication used to treat infantile spasms and a variety of inflammatory conditions. Repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is a porcine-derived, extended-release preparation of adrenocorticotropic hormone (ACTH). ACTH is a hormone in the body, which stimulates the adrenal cortex gland to secrete natural steroids (cortisol, corticosterone, and aldosterone).

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

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Policy/Criteria

Most contracts require pre-authorization approval of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) prior to coverage.

I. Continuation of therapy (COT): Repository corticotropin (Acthar Gel, Purified Cortrophin Gel) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Repository corticotropin (Acthar Gel, Purified Cortrophin Gel) may be considered medically necessary in patients with **infantile spasms (West Syndrome)** when prescribed by, or in consultation with a pediatric neurologist or an epilepsy physician specialist.

III. Administration, Quantity Limitations, and Authorization Period

- **A.** Regence Pharmacy Services considers repository corticotropin (Acthar Gel, Purified Cortrophin Gel) coverable only under the pharmacy benefit (regardless of self- or provider-administration).
- **B.** When pre-authorization is approved, repository corticotropin (Acthar Gel, Purified Cortrophin Gel) may be authorized in quantities of six-5 ml vials per month.
- **C.** Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is considered not medically necessary when used for the following conditions:

- **A.** Dermatologic diseases including severe erythema multiforme, Stevens-Johnson syndrome, systemic dermatomyositis, and polymyositis, and psoriasis.
- **B.** Multiple sclerosis, acute exacerbation in adults.
- **C.** Nephrotic syndrome, without uremia of the idiopathic type (idiopathic membranous nephropathy) or that due to lupus erythematosus.
- **D.** Ophthalmic diseases including keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation.
- **E.** Rheumatic disorders including psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis, ankylosing spondylitis.

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F. Sarcoidosis (symptomatic).

G. Serum sickness.

H. Systemic lupus erythematosus (SLE), exacerbation.

V. Repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is considered investigational when used for all other conditions.

Position Statement

- Repository corticotropin injection (Acthar and Purified Cortrophin Gel) is a purified adrenocorticotropic hormone (ACTH), available as two branded formulations:
  - Acthar Gel was first approved for sale in the United States in 1952.
  - Purified Cortrophin Gel was first FDA approved in 1954 and was widely prescribed until the 1980s but was later discontinued. In November 2021, the FDA approved a supplemental New Drug Application for reintroduction of a branded competitor to Acthar, known as Purified Cortrophin Gel (repository corticotropin injection).
- Both brands of repository corticotropin have been used in a number of different indications, though use was largely supplanted by the commercial availability of corticosteroids (e.g., hydrocortisone, prednisone, methylprednisolone), all available as much lower-cost generics.
- Intent of the policy is to cover repository corticotropin (Acthar Gel, Purified Cortrophin Gel) for infantile spasms, an indication it has demonstrated safety and efficacy (as detailed in the coverage criteria).
- Although repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is FDA approved for a variety of inflammatory conditions, these indications are grandfathered given trials establishing efficacy were not required at the time when repository corticotropin (Acthar Gel, Purified Cortrophin Gel) was originally approved. Still today, there is insufficient evidence to establish efficacy for these indications, or superiority to less costly alternatives (such as generic corticosteroids). Therefore, the use of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) for indications other than infantile spasms is considered not medically necessary. Specifically:
  - For multiple sclerosis, there is insufficient evidence to establish that repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is superior to much less costly standard of care alternatives, such as standard “pulse” methylprednisolone therapy in the management of acute exacerbations.
  - For nephrotic syndrome (idiopathic or due to lupus), there is insufficient evidence to establish that repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is superior to much less costly standard of care alternatives such as calcineurin inhibitors and cyclophosphamide, along with mycophenolate, and rituximab, all endorsed by clinical guidelines.

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- Since repository corticotropin (Acthar Gel, Purified Cortrophin Gel) stimulates steroid production in the body, the warnings of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) use is similar to those found with steroid supplementation, for example, impaired sugar tolerance and high blood sugars.
- Side effects or intolerance to corticosteroids are largely expected with the use of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) given the medication stimulates steroid production in the body.
- In addition, the evidence for significant, previously unreported safety events with the use of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is evolving. Based on the available evidence, the safety of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) relative to other therapies is unknown at this time.

Clinical Efficacy

Infantile Spasms

- There is moderate certainty that repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is safer and more effective than Sabril (vigabatrin) in the management of patients with infantile spasms (aka West syndrome), based on a high-quality systematic review (Cochrane, 2013). [1] The review concluded the following:
    * Repository corticotropin (Acthar Gel, Purified Cortrophin Gel) resulted in greater improvements in seizure frequency over 14 days compared with Sabril (vigabatrin) (76% vs 54%).
    * Repository corticotropin (Acthar Gel, Purified Cortrophin Gel) resulted in greater improvements in neurodevelopmental outcomes as measured by standardized behavioral scales.
- Repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is recognized by clinical practice guidelines as an option in the management of patients with infantile spasms, with repository corticotropin (Acthar Gel, Purified Cortrophin Gel) considered preferentially over vigabatrin. [2]

Acute Exacerbations of Multiple Sclerosis

- The use of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is considered not medically necessary when used for multiple sclerosis. Multiple sclerosis is an FDA-approved indication for repository corticotropin (Acthar Gel, Purified Cortrophin Gel); however, corticosteroids, such as methylprednisolone and dexamethasone, are less costly alternatives.
- The evidence is as follows:
    * A head-to-head clinical trial compared a 14-day course of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) with methylprednisolone 1 gm given intravenously daily for three 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). [3]

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* A high-quality systematic review concluded that there was no evidence of improved symptoms or outcomes resulting from the use of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) in the management of acute exacerbations of multiple sclerosis compared with standard "pulse" methylprednisolone therapy. [4]
* A more recent pilot trial (n=20) evaluated a 5-day course of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) for management of acute MS exacerbations. However, because the comparison was two routes of administration of repository corticotropin (intramuscular versus subcutaneous), no conclusion can be made regarding the relative benefit of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) versus other treatment options. [5]

Nephrotic Syndrome

- The use of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) is considered not medically necessary when used for nephrotic syndrome, including membranous glomerulonephropathy. Nephrotic syndrome is an FDA-approved indication; however, there are multiple less costly alternatives supported by standard of care guidelines, including corticosteroids, calcineurin inhibitors, mycophenolate, and alkylating-based therapy (cyclophosphamide). [6]
- The evidence for the use of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) for proteinuria/nephrotic syndrome is limited to retrospective case series, [7,8] one small randomized controlled trial versus standard therapy, [9] and two more recent non-controlled pilot trials and a Cochrane review of the available literature. [10-12]
    * One small randomized noninferiority trial (n=32) compared repository corticotropin (Acthar Gel, Purified Cortrophin Gel) to standard therapy of methylprednisolone in combination with cytotoxic therapy in subjects with idiopathic membranous nephropathy. Primary outcome was cumulative remission rate. Similar response was seen with standard therapy as compared to repository corticotropin. [9]
    * A small prospective, open-label, single-arm trial (n=15) evaluated repository corticotropin (Acthar Gel, Purified Cortrophin Gel) 80 units twice weekly for 6 months in subjects with resistant glomerular diseases, including membranous nephropathy, minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS), despite use of at least two prior immunosuppressants.[10] A second small Phase 2 dose-ranging pilot trial (n=20) compared repository corticotropin (Acthar Gel, Purified Cortrophin Gel) 40 and 80 units twice weekly for 12 weeks in subjects with idiopathic membranous nephropathy.[11] In both trials, repository corticotropin (Acthar Gel, Purified Cortrophin Gel) improved renal function from baseline, as defined by improvement in proteinuria; however, the lack of placebo-control limits conclusion of relative treatment effect.

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* A Cochrane systematic review (2021) of immunosuppressive treatment for adults with idiopathic membranous nephropathy concluded the following: [12]
    - Treatment options such as mycophenolate mofetil, repository corticotropin injection, rituximab and others have only been examined in a few studies.
    - There is not enough data to draw conclusions regarding their safety and effectiveness from these studies on the use of these treatments in adults with primary membranous nephropathy and nephrotic syndrome.

Other Indications

There is insufficient evidence for other indications (including, but not limited to, rheumatic disorders, systemic lupus erythematosus, dermatologic conditions, serum sickness, ophthalmic diseases, and pulmonary sarcoidosis) that treatment with repository corticotropin (Acthar Gel, Purified Cortrophin Gel) results in improved efficacy or safety when compared with other standard treatments. The evidence is limited to case reports and retrospective case series, including evidence summarized in systematic reviews for myasthenia gravis (MG), gout, and Guillain-Barré syndrome (GBS).[13-17] Therefore, use in all these indications is considered not medically necessary.

Safety [18-19]

- There is a substantial track-record of marketing experience extending over 50 years with repository corticotropin (Acthar Gel, Purified Cortrophin Gel). In pediatric patients, the length of market experience extends at least over five years.
- Common adverse reactions for repository corticotropin (Acthar Gel, Purified Cortrophin 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.
- Specific adverse reactions resulting from use of repository corticotropin (Acthar Gel, Purified Cortrophin Gel) 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 (Acthar Gel, Purified Cortrophin Gel) 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.

Dosing [18-19]

- In the treatment of infantile spasms, the recommended dose is 150 units (U)/m^2 divided into twice daily intramuscular injections of 75 U/m^2. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period.

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Cross References
BlueCross BlueShield Association Medical Policy, 5.01.17 - Repository Corticotropin Injection. [November 2021]

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Revision History

Revision Date	Revision Summary
12/07/2023	No criteria changes with this annual review.
9/23/2022	Moved coverage from medical benefit to pharmacy benefit regardless of self- or provider- administration. Effective 1/1/2023.
12/8/2021	Added Purified Cortrophin Gel, a re-introduced formulation of repository corticotrophin gel. No change to criteria or intent of policy.
1/20/2021	No changes to coverage criteria with this annual update.
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2019	No coverage criteria changes with this annual update. Clarified documentation language (no change to intent).
1/19/2018	No changes to coverage criteria with this annual update.
6/9/2017	No changes to coverage criteria with this annual update.
6/10/2016	No changes.
07/12/2013	New policy.

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