Reference number(s)
4797-A

STANDARD MEDICARE PART B MANAGEMENT

ACTHAR GEL (repository corticotropin injection)
PURIFIED CORTROPHIN GEL (repository corticotropin injection)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Acthar Gel:
   a. **Infantile Spasms:** as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age
   b. **Multiple Sclerosis:** treatment of acute exacerbations of multiple sclerosis in adults
   c. **Rheumatic Disorders:** as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); ankylosing spondylitis
   d. **Collagen Diseases:** during an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)
   e. **Dermatologic Diseases:** severe erythema multiforme, Stevens-Johnson syndrome
   f. **Allergic States:** serum sickness
   g. **Ophthalmic Diseases:** severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation
   h. **Respiratory Diseases:** symptomatic sarcoidosis
   i. **Edematous State:** to induce a diuresis or a remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus

2. Purified Cortrophin Gel:
   a. **Rheumatic Disorders**: as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); ankylosing spondylitis; acute gouty arthritis.
   b. **Collagen Diseases**: during an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).
   c. Dermatologic Diseases: severe erythema multiforme (Stevens-Johnson syndrome), severe psoriasis
   d. **Allergic States**: atopic dermatitis, serum sickness
   e. **Ophthalmic Diseases**: severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: allergic conjunctivitis, keratitis, iritis and iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation

f. **Respiratory Diseases**: symptomatic sarcoidosis
g. **Edematous States**: to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus
h. **Nervous system**: acute exacerbation of multiple sclerosis

B. Compendial Uses:
1. Diagnostic testing of adrenocortical function
2. Acquired epileptic aphasia
3. Gout

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For multiple sclerosis, nephrotic syndrome, rheumatic disorders, collagen diseases, dermatologic diseases, ophthalmic diseases, symptomatic sarcoidosis, and allergic states: chart notes detailing the outcome of the most recent trial with glucocorticoids, including dosage and duration of treatment.
B. For gout: chart notes detailing the outcome of the most recent trial with a first-line treatment option (e.g., colchicine, nonsteroidal anti-inflammatory drug [NSAIDs], or glucocorticoids), including dosage and duration of treatment.

III. EXCLUSIONS

A. Coverage of Purified Cortrophin Gel for the treatment of infantile spasms will be excluded.
B. Coverage of Acthar Gel for acute gouty arthritis, severe psoriasis, allergic conjunctivitis, and atopic dermatitis will be excluded.
C. Use of Acthar Gel in combination with Purified Cortrophin Gel will be excluded.

IV. CRITERIA FOR INITIAL APPROVAL

A. Infantile Spasms (Acthar Gel only)
Authorization of 6 months may be granted for treatment of infantile spasms in members who are less than 2 years of age.

B. Multiple Sclerosis
Authorization of 3 weeks may be granted for treatment of acute exacerbations of multiple sclerosis when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

C. Nephrotic Syndrome
Authorization of 3 months may be granted for treatment of nephrotic syndrome when repository corticotropin is requested for induction of diuresis or for remission of proteinuria in a member who has had an inadequate response to a trial of parenteral or oral glucocorticoids.

D. Rheumatic Disorders
Authorization of 3 months may be granted to members who are prescribed repository corticotropin as adjunctive treatment for rheumatic disorders (e.g., psoriatic arthritis, rheumatoid arthritis, ankylosing

spondylitis, acute gouty arthritis) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

E. Collagen Diseases
Authorization of 3 months may be granted for treatment of collagen diseases (e.g., systemic lupus erythematosus, systemic dermatomyositis, polymyositis) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

F. Dermatologic Diseases
Authorization of 3 months may be granted for treatment of dermatologic disorders (e.g., severe erythema multiforme, Stevens-Johnson syndrome, severe psoriasis) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

G. Ophthalmic Diseases
Authorization of 3 months may be granted for treatment of ophthalmic diseases (e.g., allergic conjunctivitis, keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation) when the member has had an inadequate response to a trial of parenteral, oral, or topical ophthalmic glucocorticoids.

H. Symptomatic Sarcoidosis
Authorization of 3 months may be granted for treatment of symptomatic sarcoidosis when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

I. Allergic States
Authorization of 1 month may be granted for treatment of allergic states (e.g., atopic dermatitis, serum sickness) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

J. Diagnostic Testing of Adrenocortical Function
Authorization of 1 dose may be granted to members who are prescribed repository corticotropin for diagnostic testing of adrenocortical function when the member cannot be tested with Cosyntropin.

K. Acquired Epileptic Aphasia
Authorization of 3 months may be granted for treatment of acquired epileptic aphasia.

L. Gout
Authorization of 1 month may be granted for treatment of acute gout attack when the member has had an inadequate response with a first-line treatment option (e.g., colchicine, NSAIDs, or glucocorticoids).

V. CONTINUATION OF THERAPY

A. Infantile Spasms (Acthar Gel only)
All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Acthar Gel
2. The member is receiving benefit from therapy.

B. All Other Indications

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Acthar Gel and Purified Cortrophin Gel.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Infantile spasms: A U.S. consensus report.
4. 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
5. Treatment of infantile spasms- a Cochrane Database Systematic Review
6. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis- a Cochrane Database Systematic Review
7. EFNS guidelines on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis
8. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis
9. KDIGO clinical practice guideline for glomerulonephritis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Acthar Gel and Purified Cortrophin Gel are covered in addition to the following:

1. Diagnostic testing of adrenocortical function
2. Acquired epileptic aphasia
3. Gout

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Acthar Gel or purified Cortrophin Gel to treat multiple sclerosis after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in several published studies.
Thompson and colleagues compared the efficacy of high-dose intravenous methylprednisolone with intramuscular ACTH in the treatment of acute relapse in multiple sclerosis in a double-blind, randomized, controlled study involving 61 patients. There was a marked improvement in both groups in the course of the study, but no difference between them in either the rate of recovery or the final outcome. High-dose IV methylprednisolone is a safe alternative to ACTH in the management of acute relapse in multiple sclerosis. Additionally, Berkovich and Agius indicate that while high-dose methylprednisolone is recommended to induce a faster recovery from a clinical exacerbation, ACTH is an alternative for patients who do not respond to or tolerate corticosteroids.
Frohman et al published an article discussing the treatment of MS exacerbations. They state ACTH is an alternative approach to intravenous methylprednisolone. ACTH was noted to be more expensive than steroids,

have more side effects, and gives less consistent results. ACTH can be used when a patient is unresponsive to corticosteroids or in cases in which ACTH's positive effects on bone via stimulation of dehydroepiandrosterone and mineralocorticoids may be desirable.

Support for using Acthar Gel or purified Cortrophin Gel to treat nephrotic syndrome after an in adequate response to a trial of parenteral or oral glucocorticoids can be found in a prospective trial by Bomback and colleagues. Fifteen subjects with resistant glomerular diseases were treated with ACTH gel (80 units subcutaneously twice weekly) for 6 months. Resistant membranous nephropathy (MN), minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS) were defined as failure to achieve sustained remission of proteinuria off immunosuppressive therapy with at least 2 treatment regimens (one of which was a corticosteroid); resistant IgA nephropathy was defined as >1 g/g urine protein:creatinine ratio despite maximally tolerated RAAS blockade. Remission was defined as stable or improved renal function with ≥50% reduction in proteinuria to <0.5 g/g (complete remission) or 0.5-3.5 g/g (partial remission). The study included 5 subjects with resistant idiopathic MN, 5 subjects with resistant MCD (n = 2)/FSGS (n = 3), and 5 subjects with resistant IgA nephropathy. Two resistant MN subjects achieved partial remission on ACTH therapy, although 3 achieved immunologic remission of disease (PLA(2)R antibody disappeared by 4 months of therapy). One subject with resistant FSGS achieved complete remission on ACTH; one subject with resistant MCD achieved partial remission but relapsed within 4 weeks of stopping ACTH. Two subjects with resistant IgA nephropathy demonstrated >50% reductions in proteinuria while on ACTH, with proteinuria consistently <1 g/g by 6 months. Three of 15 subjects reported significant steroid-like adverse effects with ACTH, including weight gain and hyperglycemia, prompting early termination of therapy without any clinical response.

Support for using Acthar Gel or purified Cortrophin Gel to treat rheumatic disorders after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in the package insert and several guidelines. In the 2012 American College of Rheumatology Guidelines for Management of Gout, ACTH should be used in patients unable to take oral corticosteroids as an alternative to intra-articular, intravenous, or intramuscular corticosteroids.

Support for using Acthar Gel or purified Cortrophin Gel to treat collagen diseases after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in a published retrospective case series by Levine. Five patients were described, all of whom received oral or parenteral corticosteroids prior to using ACTH. The patients tolerated ACTH for up to three months with no significant side effects and no need to taper therapy. The author concludes that ACTH should be considered as an option for refractory dermatomyositis and polymyositis.

Patel and colleagues (2016) stated that idiopathic inflammatory myopathies are a group of systemic autoimmune diseases that involve inflammation of skeletal muscle. The 2 most common forms are dermatomyositis and polymyositis, the former of which entails a skin component. There are few approved therapeutics available for treatment of this group of diseases and the first-line therapy is usually corticosteroid treatment. Considering that a large proportion of patients do not respond to or cannot tolerate corticosteroids, additional treatments are needed. There are second-line therapies available, but many patients are also refractory to those options. H.P. Acthar Gel (repository corticotropin injection [RCI]) is a melanocortin peptide that can induce steroid-dependent effects and steroid-independent effects. These researchers presented a series of cases that involved the use of RCI in the management of dermatomyositis and polymyositis; RCI treatments resulted in improvement in 3 of 4 patients, despite failure with previous therapies. The use of RCI did not exacerbate any co-morbidity and no significant changes in blood pressure, weight, or glycemic control were observed. The authors concluded that these findings were encouraging and suggested that RCTs applying RCI to dermatomyositis and polymyositis are needed.

In an open-label, clinical trial, Aggarwal and colleagues (2018) evaluated the safety, efficacy, tolerability and steroid-sparing effect of RCI in refractory adult polymyositis (PM) and dermatomyositis (DM). Adults with refractory PM and DM were enrolled by 2 centers. Inclusion criteria included refractory disease defined as failing glucocorticoid and/or greater than or equal to 1 immunosuppressive agent, as well as active disease

defined as significant muscle weakness and greater than 2 additional abnormal core set measures (CSMs) or a cutaneous 10 cm visual analog scale (VAS) score of greater than or equal to 3 cm and at least 3 other abnormal CSMs. All patients received RCI of 80 units subcutaneously twice-weekly for 24 weeks. The primary end-point was the International Myositis Assessment and Clinical Studies definition of improvement. Secondary end-points included safety, tolerability, steroid-sparing as well as the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism myositis response criteria (EULAR); 10 of the 11 enrolled subjects (6 DM, 4 PM) completed the study; 7 of 10 met the primary end-point of efficacy at a median of 8 weeks. There was a significant decrease in prednisone dose from baseline to conclusion (18.5 (15.7) versus 2.3 (3.2); $p < 0.01$). Most individual CSMs improved at week 24 compared with the baseline, with the muscle strength improving by greater than 10% and the physician global by greater than 40%; RCI was considered safe and tolerable. No patient developed significant weight gain or an increase of hemoglobin A1c or Cushingoid features. The authors concluded that treatment with RCI was effective in 70% of patients, safe and tolerable, and led to a steroid dose reduction in patients with adult myositis refractory to glucocorticoid and traditional immunosuppressive drugs. This was an open-label study with small sample size (n = 10); these preliminary findings need to be validated in well-designed studies.

Support for using Acthar Gel or purified Cortrophin Gel to treat dermatologic diseases after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in a case series. Brown (2016) stated that although numerous therapeutic options are available for patients with psoriatic arthritis (PsA), a need for effective and tolerable treatments remains for patients with refractory disease who have failed previous therapies and continue to experience tender and/or swollen joints, pain, and disease activity. Repository corticotropin injection is believed to produce steroidogenic, steroid-independent, anti-inflammatory, and immunomodulatory effects in patients with rheumatic disorders, such as PsA. Limited literature exists on the use of RCI in patients with refractory PsA. In a case-series study, this investigator provided information on the clinical features of patients with refractory PsA and their response to RCI. A total of 9 patients treated with RCI for refractory PsA were retrospectively identified and included in the case series. All 9 patients experienced at least transient improvements in their active skin and joint disease. In some patients, it was necessary to titrate the RCI to an appropriate dose; RCI was used in some patients to bridge with another PsA therapy, such as apremilast or certolizumab; RCI was well-tolerated but discontinued in 3 patients due to pre-existing conditions (hypertension and hyperglycemia). The author concluded that RCI may be a safe and effective option for patients with refractory PsA who failed therapy with multiple previous treatments. These preliminary findings need to be validated by well-designed studies.

Support for using Acthar Gel or purified Cortrophin Gel to treat ophthalmic disease after a trial of parenteral, oral or topical ophthalmic glucocorticoids can be found in a phase four, multicenter, open-label study. Wirta et al (2022) stated that non-infectious keratitis is a painful corneal inflammation treated with topical cyclosporine and other immunosuppressants. Additional therapeutic options are needed for keratitis that does not improve with standard therapies. In an open-label, multi-center, phase-IV clinical trial, these researchers examined the safety and effectiveness of RCI for the treatment of refractory severe non-infectious keratitis. Patients were 18 years of age or older with persistent severe keratitis despite treatment with topical immunosuppressants. Patients received 80 U of RCI subcutaneously twice-weekly for 12 weeks followed by a 4-week taper. Assessments included all domains of the Impact of Dry Eye on Everyday Life (IDEEL) Questionnaire, Ocular Discomfort and 4-Symptom Questionnaire, and VAS. Corneal fluorescein and conjunctival lissamine green staining, Conjunctival Redness Scale, Schirmer's test, VA, slit lamp examination, and IOP were also examined. Safety was evaluated via treatment-related AEs. Analyses were carried out using the modified intent-to-treat (mITT) population (patients who received 1 dose or more of RCI and contributed any post-baseline effectiveness data). In the mITT population (n = 35), 50.0% (95% confidence interval [CI]: 33.2% to 66.8%) of patients experienced clinically important improvements in the symptom bother domain of the IDEEL Questionnaire at week 12 of RCI therapy. All domains of the IDEEL and the Ocular Discomfort and 4-Symptom Questionnaire showed improvements at week 12 of RCI treatment. The most pronounced improvements in the VAS at week 12 were for eye dryness and eye discomfort. Corneal staining, conjunctival

staining, conjunctival redness, and tear production showed early improvements that were sustained through week 12. No new safety signals for RCI were identified. The authors concluded that RCI was safe and effective for refractory severe non-infectious keratitis that has not improved with other approved therapies.

These researchers stated that the findings of this study added to the body of literature for a condition that is still being examined extensively. They noted that drawbacks of this study included a relatively small sample size (n = 35), a short treatment period of 12 weeks, and a lack of a placebo comparator. However, because the patients were not permitted to receive standard therapies such as cyclosporine, lifitegrast, and corticosteroids during the study period, the observed improvements in the symptoms of keratitis were likely the result of RCI treatment. Moreover, these investigators stated that although the open-label study design was appropriate for this target population of patients with severe refractory keratitis, the safety and effectiveness of this treatment warrant further investigation in a randomized, placebo-controlled trial.
Additionally, Anesi and colleagues (2023) examined if subcutaneous RCI (Acthar gel) could be an effective potential therapeutic agent for non-infectious retinal vasculitis. Patients with active retinal vasculitis were followed with serial ultra-wide-field fluorescein angiograms and treated with 80 units of subcutaneous repository corticotropin injection twice-weekly. Primary outcome of greater than or equal to 50 % improvement in response level (RL) for retinal vasculitis and percent improvement in retinal vasculitis severity scoring (RVSS) by more than one quartile (greater than or equal to 25 %) at week 12 was met in 15 and 16 of the 30 total eyes, respectively, including 1 eye with severe retinal vasculitis in each group. Complete resolution of retinal vasculitis was observed in 7 eyes with a mean time of 17.1 weeks. Intra-ocular pressure (IOP) elevation requiring therapy and cataract progression were noted in 2 and 3 eyes, respectively; 1 patient stopped medication due to side effects (injection site reaction). The authors concluded that repository corticotropin injection was well-tolerated overall; it may be an effective therapeutic agent in the treatment of non-infectious retinal vasculitis. Moreover, these researchers stated that these findings should be validated with further well-designed studies with larger sample sizes.

The authors stated that this study had several drawbacks, which include its open-label status, a limited study period of only 24 weeks, the lack of a control population, varied etiology and severity of disease, concomitant use of other immunomodulatory medications, as well as the use of subjects either on or off these other forms of therapy. Participants of this study represented a variable group of disease processes that had retinal vasculitis, as might be expected in a condition or population being studied where the number of patients is few. Criticism could be made to this point of the validity of any conclusions brought forth in this study, however, with the etiology of these processes being at least agreeably non-infectious in nature, these investigators expected that these data contain merit in the way of an observed response of a non-infectious inflammatory process to a single given therapy. Lastly, although this trial was carried out with funding provided by “Mallinckrodt Pharmaceuticals, Bedminster, NJ”, the authors were solely responsible for protocol development, initiation of patient recruitment, administration of study protocol, as well as manuscript production.

Support for using Acthar Gel or purified Cortrophin Gel to treat symptomatic sarcoidosis after an inadequate trial or parenteral or oral glucocorticoids can be found in a study by Chopra and colleagues (2019). The authors stated that RCI (repository corticotropin injection) has regulatory approval for many indications, including symptomatic sarcoidosis. This large case-series study of patients with advanced symptomatic sarcoidosis treated with RCI described patient characteristics, utilization patterns, concomitant therapies, and physicians' assessments of treatment response. This trial included patients greater than or equal to 18 years of age and with symptomatic sarcoidosis who were treated with RCI in the previous 36 months and had completed a course of RCI or received RCI for greater than or equal to 6 months at the time of data collection. The study included 302 patients (mean age of 51 years; 52%, women) with a mean 4.8 years since initial diagnosis of sarcoidosis. Most patients (76%) had extra-pulmonary involvement, primarily in the skin (28%), joints (25%), heart (22%), and eyes (22%); 34% had multiple (greater than or equal to 2) organ involvement. The mean duration of RCI treatment was 32.5 weeks, with 61.6% of patients continuing RCI therapy for greater than or equal to 6 months. The RCI utilization pattern indicated an individualized approach to therapy,

with a higher starting dose associated with a shorter duration of therapy compared with a lower starting dose. The percentage of patients who used corticosteroids decreased from 61.3% during the 3 months before initiation of RCI to 12.9% 3 months following RCI therapy; the mean daily dose of corticosteroid decreased from 18.2 mg to 9.9 mg. The proportion of patients given less than 10 mg/day of prednisone increased from 21% before RCI use to 47% 3 months after RCI use. According to physicians' assessments of change in patients' health status following RCI therapy, overall status improved in 95 % of patients, overall symptoms in 73%, lung function in 38%, and inflammation in 33%. The authors concluded that these findings suggested that RCI is a viable therapeutic option for patients with advanced symptomatic sarcoidosis and provided insights on patient characteristics and practice patterns to help clinicians determine appropriate use.

The authors stated that this study was limited by its reliance on data retrospectively collected via a survey of respondents who had access to patient medical records, which might have had errors and omissions. These investigators tried to minimize the impact of potential missing data by focusing on patients' clinical aspects and physicians' assessments, the types of information that are usually readily available in medical records or best known to the respondents who submitted data for this study. The study did not quantify patients' outcomes such as diagnostic measurements and safety end-points. Furthermore, because of its inherent retrospective design, there may be a risk of bias, resulting in over-estimation of the effectiveness of RCI based on physicians' assessments. Because this was an exploratory and hypothesis-generating study, these researchers did not make any comparisons between RCI and a control group or other treatments, which may also result in bias. It is important to note the following: RCI is indicated for symptomatic sarcoidosis; RCI is included in treatment guidelines from the Foundation for Sarcoidosis Research; and a randomized, phase-IV, double-blind, placebo-controlled clinical trial is ongoing to examine the safety and efficacy of Acthar gel in patients with pulmonary sarcoidosis. Another limitation was the use of the physicians' assessments of improvement in a patient's health status as a key descriptive end-point to evaluate RCI therapy. This subjective end-point relied on each individual physician's interpretation of each patient's medical record and the physician's standards for assessing improvement. These researchers did not collect data on test results or other objective measures that physicians might have used to make their determinations. The retrospective and non-comparative study design did not allow the authors to discern whether patients were responding to known concomitant treatments or to therapies not known to the physician or not recorded in the medical records. The use of physicians' assessment may have under-estimated the use of biologics in these patients; however, this could not be fully ascertained from the present study.

Support for using parenteral or oral glucocorticoids be found in several guidelines and the package insert. The American Academy of Allergy, Asthma and Immunology and the Joint Council of Allergy, Asthma and Immunology state systemic corticosteroids orally or intravenous may be necessary in severe cases of serum sickness. For atopic dermatitis, the American Academy of Dermatology and European guidelines for the treatment of atopic dermatitis (2018) both agree using corticosteroids is acceptable for acute flares but long-term oral corticosteroids are not recommended.

Support for using Acthar Gel or purified Cortrophin Gel for diagnostic testing of adrenocortical function can be found in the American Hospital Formulary Service-Drug Information (AHFS-DI) reference. Acthar Gel and purified Cortrophin Gel can be used as an aid in the diagnosis of adrenocortical insufficiency. The 30-minute cosyntropin test provides a good method of screening for primary adrenocortical insufficiency (Addison's disease) and is preferable to corticotropin for rapid screening since it is less likely to cause allergic reactions. When a greater stimulus to the adrenal cortex is desired, corticotropin or cosyntropin may be administered by IV infusion. If subnormal increases in plasma cortisol concentrations occur following administration of corticotropin or cosyntropin, additional tests providing prolonged stimulation of the adrenal cortex are required before impaired adrenocortical function can be diagnosed precisely and differentiation between primary and secondary adrenocortical insufficiency can be established.

Support for using Acthar Gel or purified Cortrophin Gel to treat acquired epileptic aphasia can be found in a case study reported by Lerman, Lerman-Sagie, and Kivity. Corticotropin 80 units/day was given for 3 months; after 3 weeks of treatment electroencephalographic results improved and after 6 months speech returned. When after 2 years the aphasia recurred corticotropin was immediately reinstituted; within a few weeks speech and electroencephalogram returned to normal. Landau-Kleffner syndrome is a rare syndrome of childhood characterized by an acquired aphasia associated with abnormal electroencephalogram, with about two-thirds of cases also exhibiting seizure activity.

Support for using Acthar Gel or purified Cortrophin Gel to treat gout can be found the gout guidelines from the American College of Rheumatology. Colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or IM) are recommended as first-line treatment for gout flares over adrenocorticotropic hormone (ACTH). For patients who cannot take medications by mouth, glucocorticoids (IM, IV, or intraarticular) are recommended over ACTH, although subcutaneous synthetic ACTH is a suggested alternative.

VIII. REFERENCES

1. Acthar Gel [package insert]. Bedminster, NJ: Mallinckrodt ARD LLC.; October 2021.
2. DRUGDEX® System (electronic version). IBM Watson Health, Greenwood Village, Colorado. Available at http://www.micromedexsolutions.com. Accessed May 4, 2023.
3. American Society of Health System Pharmacists. AHFS Drug Information. Bethesda, MD. Electronic Version 2020. http://www.online.lexi.com. Accessed May 4, 2023.
4. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: A U.S. consensus report. *Epilepsia*. 2010:51:2175-2189.
5. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2012;78:1974-1980.
6. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. *Cochrane Database Syst Rev*. 2013;6:CD001770.
7. Riikonen R. Recent advances in pharmacotherapy of infantile spasms. *CNS Drugs* 2014; 28:279-290.
8. Pavone P, et al. Infantile spasms syndrome, West Syndrome and related phenotypes: what we know in 2013. *Brain & Development* 2014; 739-751.
9. Citterio A, La Mantia L, Ciucci G, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. *Cochrane Database Syst Rev 4*:CD001331.
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; 39:969-971.
11. Berkovich R, Agius MA. Mechanisms of action of ACTH in the management of relapsing forms of multiple sclerosis. *Ther Adv Neurol Disord* 2014; 7(2):83-96.
12. Frohman EM, Shah A, Eggenberger E, et al. Corticosteroids for multiple sclerosis: I. Application for treatment exacerbations. *Neurotherapeutics* 2007; 4(4): 618-626.
13. Sellebjerg F, Barnes D, Filippini G, at al. EFNS guidelines on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis. *European Journal of Neurology* 2005; 12:939-946.
14. Bomback AS, Canetta PA, Beck Jr LH, et al. Treatment of resistant glomerular diseases with adrenocorticotropic hormone gel: a prospective trial. *Am J Nephrol* 2012; 36:58-67.
15. Hladunewich MA, Cattran D, Beck LH, et al. A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (H.P. Acthar Gel) in nephrotic syndrome due to idiopathic membranous nephropathy. *Nephrol Dial Transplant* 2014; 29:1570-1577.
16. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care & Research* 2012; 64(6):797-808.

17. KDIGO clinical practice guideline for glomerulonephritis. *Kidney International Supplements* 2012; 2(2): 259-274.
18. Tran TH, Hughes GJ, Greenfeld C, et al. Overview of current and alternative therapies for idiopathic membranous nephropathy. *Pharmacotherapy* 2015; 35(4):396-411.
19. Mouterde G, Dernis E, Ruyssen-Witrand A, et al. Indications of glucocorticoids in early arthritis and rheumatoid arthritis: recommendations for clinical practice based on data from the literature and expert opinion. *Joint Bone Spine* 2010; 77:597-603.
20. Levine T. Treating refractory dermatomyositis or polymyositis with adrenocorticotropic hormone gel: a retrospective case series. *Drug Design, Development and Therapy* 2012; 6:133-139.
21. Purified Cortrophin Gel [package insert]. Baudette, MN: ANI Pharmaceuticals, Inc.; January 2022.
22. Lerman P, Lerman-Sagie T, & Kivity S: Effect of early corticosteroid therapy for Landau-Kleffner syndrome. Dev Med Child Neurol 1991; 33:257-266.
23. FitzGerald JD, Dalbeth N, Mikuls T, et al: 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken) 2020; 72(6):744-760.
24. Khanna D , Khanna PP , Fitzgerald JD , et al: 2012 American College of Rheumatology guidelines for management of gout. Part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken) 2012; 64(10):1447-1461.
25. Patel A, Seely G, Aggarwal R. Repository corticotropin injection for treatment of idiopathic inflammatory myopathies. Case Rep Rheumatol. 2016;2016:9068061.
26. Aggarwal R, Marder G, Koontz DC, et al. Efficacy and safety of adrenocorticotropic hormone gel in refractory dermatomyositis and polymyositis. Ann Rheum Dis. 2018;77(5):720-727.
27. Brown AN. Repository corticotropin injection in patients with refractory psoriatic arthritis: A case series. Open Access Rheumatol. 2016;8:97-102.
28. Chopra I, Qin Y, Kranyak J, et al. Repository corticotropin injection in patients with advanced symptomatic sarcoidosis: Retrospective analysis of medical records. Ther Adv Respir Dis 2019;13:1753466619888127.
29. Wollenberg A, Barbarot S, Bieber T, et al. European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), the European Academy of Allergy and Clinical Immunology (EAACI), the European Task Force on Atopic Dermatitis (ETFAD), European Federation of Allergy and Airways Diseases Patients' Associations (EFA), the European Society for Dermatology and Psychiatry (ESDaP), the European Society of Pediatric Dermatology (ESPD), Global Allergy and Asthma European Network (GA2LEN) and the European Union of Medical Specialists (UEMS). Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol. 2018 Jun;32(6):850-878. doi: 10.1111/jdv.14888. PMID: 29878606.
30. Schneider L, Tilles S, Lio P, Boguniewicz M, et al. Atopic dermatitis: a practice parameter update 2012. J Allergy Clin Immunol. 2013 Feb;131(2):295-9.e1-27. doi: 10.1016/j.jaci.2012.12.672. PMID: 23374261.
31. Anesi SD, Chang PY, Maleki A, et al. Treatment of noninfectious retinal vasculitis using subcutaneous repository corticotropin injection. J Ophthalmic Vis Res. 2021;16(2).
32. Anesi SD, Chang PY, Maleki A, et al. Effects of subcutaneous repository corticotropin gel injection on regulatory T cell population in noninfectious retinal vasculitis. Ocul Immunol Inflamm. 2023;31(3):556-565.
33. Wirta D, McLaurin E, Ousler G, et al. Repository corticotropin injection (Acthar ® gel) for refractory severe noninfectious keratitis: Efficacy and safety from a phase 4, multicenter, open-label study. Ophthalmol Ther. 2021;10(4):1077-1092.
34. Khanna D , Khanna PP , Fitzgerald JD , et al: 2012 American College of Rheumatology guidelines for management of gout. Part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken) 2012; 64(10):1447-1461.

