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Prior Authorization Review: repository corticotropin injection (HP Acthar Gel for Injection)

Background:
Adrenocorticotropin hormone (ACTH) is secreted by the pituitary gland and stimulates the adrenal cortex to secrete cortisol, aldosterone and other hormones. Repository corticotropin injection, an ACTH analog, is available as an injectable gel that must be administered via intramuscular or subcutaneous routes. Corticotropin injection is indicated as monotherapy for the treatment of infantile spasms (West Syndrome) in infants and children under the age of 2 years.[1] It is also indicated for the treatment of multiple sclerosis exacerbations in adults.[1] Other FDA-approved indications include treatment of rheumatic, collagen, dermatologic, allergic, ophthalmic, respiratory, and edematous disorders.[1] The adverse effects of corticotropin are related to its steroidogenic effects and are similar to those of corticosteroids.[1] Corticotropin is contraindicated for patients with porcine protein hypersensitivity, scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history or presence of a peptic ulcer, congestive heart failure, adrenocortical hypofunction, and uncontrolled hypertension.[1]

Corticotropin injection was previously reviewed by the P and T committee in March 2013. Conclusions from that review were as follows:

- There remains very low to insufficient evidence for the treatment of infantile spasms. Most trials are open label or retrospective analysis.
- There is low quality evidence that ACTH may be effective and that vigabatrin is possibly effective for the short term treatment of infantile spasms; however, there remains insufficient evidence if treatment will result in better long-term developmental outcomes.
- There is insufficient evidence to support the use of repository corticotropin injection in the use of aiding in the diagnosis of adrenocortical insufficiency and this indication was removed from the product label in 2010.
- There is insufficient evidence comparing repository corticotropin injection in corticosteroid responsive disorders and no evidence proving superior efficacy or safety to systemic corticosteroids. Available evidence is based on retrospective analyses and case series.
- There is low quality evidence that ACTH is beneficial compared to placebo in improving the symptoms of MS acute exacerbations and insufficient evidence that treatment with ACTH prevents new exacerbations or reduces long term disability.
- There is insufficient evidence demonstrating a difference in rate of recovery between high dose glucocorticoids and ACTH in the treatment of MS exacerbations. ACTH may be an option in those patients who cannot tolerate steroids.
- There is insufficient evidence to support the use of repository corticotropin injection in conditions not responsive to corticosteroid therapy (tobacco cessation, acute gout, childhood epilepsy)

Infantile Spasms (West Syndrome):
West syndrome is form of infant epilepsy characterized by spasms, hypsarrhythima detected on EEG, and psychomotor delay.[2] Approximately two thirds of infants with West syndrome will have an underlying neurologic abnormality.[2] The incidence of infantile spasms is estimated as 2-3 infants per 10,000 live births.[2] Effective treatments have been difficult to identify due to adverse reactions, incomplete response rates, and variable availability of treatments in different countries.[3] Three therapies are presently utilized to manage infantile spasms: ACTH, vigabatrin, and oral corticosteroids. [4] The mechanism of action of ACTH in treating infantile spasms is not known.[1]

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The Cochrane Collaboration updated a review in 2013 of pharmacotherapeutic agents for treatment of infantile spasms.[3] The analysis included 18 RCTs in 858 patients treated with 12 different medications.[3] Drugs assessed in the RCTs included: ACTH (9 different treatment regimens and preparations), hydrocortisone, prednisone, prednisolone, vigabatrin, magnesium sulfate, nitrazepam, valproate, sulthiame, flunarizine, ganaxolone methysergide, and alpha-methylparatyrosine. Outcome measures included: cessation of spasms, quantitative reduction of spasms, resolution of EEG abnormality, relapse rates, long-term psychomotor development, subsequent epilepsy rates, adverse effects and mortality.[3] Interventions varied by choice of medication, dose, frequency, route of administration and length of treatment. The authors rated the overall quality of the studies as poor due to a small numbers of participants, inadequate power, and unclear methods of randomization, inadequate concealment of allocation, unclear blinding techniques, and loss to follow-up. The authors concluded that ACTH, prednisolone, and tetracosactide depot resolve spasms faster than vigabatrin, but it is not clear if this improves long-term outcomes. The optimum dose of ACTH (150 units/m^2/day vs. 20-30 units/day) is not clear. The FDA approved recommended dose is 150 units/m^2 divided into twice daily intramuscular injections of 75 u/m^2 for 2 weeks.[1] After 2 weeks the dose should be gradually tapered and discontinued over a 2 week period.[1] More research is needed with robust methodology and detailed reporting to clarify optimal pharmacotherapy for management of infantile spasms.

A task force for the Commission of Pediatrics developed consensus recommendations for management of infantile seizures in 2015. Child neurologists were recruited from the International League Against Epilepsy (ILAE). [5] The task force found that evidence was limited due to inconsistency amongst studies, poor study design, and small study sizes. Treatment recommendations were based on low quality evidence and were often based on expert opinion:[5]

- ACTH is preferable in the short-term control of spasms (level B evidence)*
- Oral corticosteroids are probably effective for short-term control of spasms (level C evidence)*
- Data are insufficient to comment on the optimal preparation, dosage, and duration of treatment of corticosteroids (level U evidence)*
- Low-dose ACTH (20-30 IU) may be considered as an alternative to high-dose ACTH (150 IU/m^2) for treatment of epileptic spasms (level B evidence)*
- Vigabatrin is possibly effective in the short-term control of spasms (level C evidence), especially in the case of tuberous sclerosis complex (level C evidence)*

  **American Academy of Neurology Practice parameters: Strength of the practice recommendation based on the reviewed literature*[6]
  - *Level A Established as effective, ineffective, or harmful, or as useful/predictive or not useful/predictive*
  - *Level B Probably effective, ineffective, or harmful, or as useful/predictive or not useful/predictive*
  - *Level C Possibly effective, ineffective, or harmful, or as useful/predictive or not useful/predictive*
  - *Level U Data are inadequate or conflicting; treatment, test or predictor unproven*

Multiple Sclerosis:
No new evidence regarding the use of corticotropin in multiple sclerosis has been published since the last review in 2013.

Other Indications:
No new evidence regarding the use of corticotropin in rheumatic, collagen, dermatologic, or ophthalmic diseases has been published since the last review in 2013.

There were no claims for corticotropin in the Oregon Health Plan Fee-for-Service population during 2015.

Recommendations:
No changes to the current Prior Authorization (PA) criteria are recommended.

References:

1. Acthar Gel (repository corticotropin injection). Hazelwood, MO: Mallinckrodt Pharmaceuticals. January 2015.

2. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. *Epilepsia*. 2010; 51(10):2175-2189. doi:10.1111/j.1528-1167.2010.02657.x.

3. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. [Review][Update of Cochrane Database Syst Rev. 2008 ;(4):CD001770; PMID: 18843624]. *Cochrane Database of Systematic Reviews*. 2013. doi:10.1002/14651858.CD001770.pub3.

4. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2012; 78(24):1974-1980. doi:10.1212/WNL.0b013e318259e2cf.

5. 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; 56(8):1185-1197. doi:10.1111/epi.13057.

6. Edlund, W, et.al, American Academy of Neurology, 2004 AAN Process Manual.pdf. ww.aan.com/uploadedFiles/Website_Library_Assets/Documents/2.Clinical_Guidelines/4.About_Guidelines/1.How_Guidelines_Are_Developed/.pdf. Accessed June 9, 2016.

Repository Corticotropin Injection

Goal(s):

- To restrict use to patient populations in which corticotropin has been shown to be effective and safe.

Length of Authorization:

4 weeks

Requires PA:

- Repository Corticotropin Injection

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis monotherapy for infantile spasms in infants and children under 2 years of age?	**Yes:** Approve up to 4 weeks (2 weeks of treatment and 2-week taper)	**No:** Go to #3
3. Is the diagnosis for acute exacerbation or relapse of multiple sclerosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and been unable to tolerate intravenous methylprednisolone or high-dose oral methylprednisolone?	**Yes:** Approve up to 5 weeks (3 weeks of treatment, followed by 2-week taper).	**No:** Go to #5

Approval Criteria		
5. Is the prescription for adjunctive therapy for short-term administration in corticosteroid-responsive conditions, including: • The following rheumatic disorders: psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis or ankylosing spondylitis; **OR** • The following collagen diseases: systemic lupus erythematosus or systemic dermatomyositis; **OR** • Dermatologic diseases such as erythema multiforme or Stevens-Johnson syndrome; **OR** • Ophthalmic diseases such as keratitis, iritis, uveitis, optic neuritis, or chorioretinitis; **OR** • For the treatment of respiratory diseases, including symptomatic sarcoidosis or for treatment of an edematous state?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is there a contraindication, intolerance, or therapeutic failure with at least one intravenous corticosteroid?	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *11/16 (DM); 5/13*
Implementation: *1/1/14*