Medical Policy

BlueCross BlueShield of Kansas
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Title: H.P. Acthar Gel (repository corticotropin)

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/15-17_predeterm_request_frm.pdf
BCBSKS will review Prior Authorization requests effective May 22, 2013.

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.htm

For information concerning Prior Authorization Prescription Drugs:
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior_authorization.htm

Professional
Original Effective Date: July 1, 2012
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Institutional
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If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

Repository corticotropin intramuscular or subcutaneous injection is primarily used for treating infantile spasms (West syndrome). It has also been investigated for diagnostic testing of adrenocortical function and for treating a variety of other conditions.

Repository corticotropin injection (H.P. Acthar® Gel, Questcor, Union City, CA) is a purified, sterile preparation of the natural form of adrenocorticotropic hormone (ACTH) in gelatin to provide a prolonged release after intramuscular or subcutaneous injection. ACTH works by stimulating the adrenal cortex to produce cortisol, corticosterone, and a number of other hormones.

According to the 2010 product information (product labeling), repository corticotropin injection may be used in the treatment of the following conditions (1):

1.1 Infantile Spasms:

Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.

1.2 Multiple Sclerosis:

Treatment of acute exacerbations of multiple sclerosis in adults.

1.3 Rheumatic Disorders:

Indicated 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.

1.4 Collagen Diseases:

During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).

1.5 Dermatologic Diseases:

Indicated for treatment of severe erythema multiforme, Stevens-Johnson syndrome.

1.6 Allergic States:

Serum sickness.

1.7 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.

1.8 Respiratory Diseases:

Symptomatic sarcoidosis

1.9 Edematous State:
To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that is due to lupus erythematosus.

Contraindications for use of this agent include scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin.

Unlike previous versions, the 2010 product label does not mention the use of repository corticotropin injection for diagnostic testing of adrenocortical function.

West Syndrome/Infantile Spasms
West syndrome is a rare epileptic disorder of early infancy (90% of cases are diagnosed the first year of life) consisting of three main characteristics; infantile spasm, mental retardation, and hypsarrhythmia, a specific abnormal pattern on electroencephalogram (EEG). Often the term “infantile spasms” is used synonymously with West syndrome. Infantile spasms are characterized by an initial contraction phase followed by a more sustained tonic phase.

Other treatments for infantile spasms include:
Vigabatrin (Sabril®, Lundbeck, Inc.) oral solution is another available treatment for infantile spasms. Sabril is indicated as monotherapy for pediatric patients with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss.

Cosyntropin (Cortosyn®, Amphastar), a synthetic form of ACTH, is created by isolating the first 24 amino acids from ACTH peptide. Unlike the natural form of ACTH, which is given intramuscularly or subcutaneously, Cortosyn should only be given intravenously. A depot formulation of cosyntropin (Synacthen Depot) is not approved by the U.S. Food and Drug Administration (FDA) for treating infantile spasms. However, it is available through a compassionate-use program through the specialty pharmacy Caligor Rx in New York.

Regulatory Status
H.P. Acthar Gel was approved by the FDA in 1952. Clinical efficacy and safety data for the majority of indications, with the exception of infantile spasm and multiple sclerosis 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.

In December 2008, Questcor resubmitted a supplemental new drug application (sNDA) for H.P. Acthar gel (repository corticotrophin) injection to the FDA for treating infantile spasms. Approval was granted in October 2010.

POLICY

A. Repository corticotropin injection may be considered **medically necessary** for treatment of infantile spasms (West syndrome), when the patient is < 24 months of age.

B. Use of repository corticotropin injection is considered **not medically necessary** as treatment of corticosteroid-responsive conditions, except when:
   1. There are medical contraindications or intolerance to corticosteroids that are not also expected to occur with use of repository corticotropin injection. This may include, but not be limited to: Multiple Sclerosis, Rheumatic disorders, Collagen diseases, Dermatologic diseases, Allergic states, Ophthalmic diseases, Respiratory diseases, or Edematous state.
      OR
   2. There has been an incomplete response to an adequate trial of corticosteroids.

C. Repository corticotropin injection is considered **not medically necessary** for use in diagnostic testing of adrenocortical function.

D. Except as noted here, use of repository corticotropin injection is considered **experimental / investigational** for conditions that are not responsive to corticosteroid therapy including, but not limited to, use in tobacco cessation, acute gout, and childhood epilepsy.

Length of Approval: 6 months

Policy Guidelines

1. Repository corticotropin injection is one of the agents that can be considered for treatment of infantile spasms as noted in the Rationale section.

2. The product information material makes the following comments about dosage:
   - In the treatment of infantile spasms, the recommended dose is 150 U/m2 divided into twice daily intramuscular injections of 75 U/m2. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period.
   - In the treatment of other disorders and diseases, dosing will need to be individualized depending on the disease under treatment and the medical condition of the patient. It may be necessary to taper the dose.
   - repository corticotropin is generally more costly than alternative agents but has not been shown to lead to improved outcomes compared to those obtained with alternatives for some indications

RATIONALE

Infantile spasms

Data for use of repository corticotropin injection was summarized in a 2004 practice parameter from the American Academy of Neurology. (2) While this review concluded that repository corticotropin injection is "probably an effective agent in the short-term treatment of infantile spasms," evidence for repository corticotropin injection was stronger than for any other pharmacologic agent. The report also indicates that there is insufficient evidence to determine whether oral corticosteroids are effective and that vigabatrin was possibly effective but that there are concerns about retinal toxicity. This report also notes that the impact of treatment of seizures/spasms on long-term patient outcomes is unknown.

In 2008, Hancock et al. authored a Cochrane review (3) to compare the effects of single drugs used to treat infantile spasms in terms of long-term psychomotor development, subsequent epilepsy, control of the spasms, and adverse effects. Eleven randomized controlled trials (RCTs) (n=514) were included and tested 8 different drugs. Overall, methodology of the studies was poor. No study assessed long-term psychomotor development or onset of other seizure types. The authors concluded that "We found no single treatment to be proven to be more efficacious in treating infantile spasms than any of the others (other than vigabatrin in the treatment of infantile spasms in tuberous sclerosis in one underpowered study). Few studies considered psychomotor development or subsequent seizure rates as outcomes and none had long-term follow-up. Further trials with larger numbers of participants, and longer follow-up are required."

Other notable conclusions of the Cochrane review are:

- The strongest evidence suggests that hormonal treatment (prednisone, tetrocosactide (synthetic ACTH [cosyntropin]) and ACTH [adrenocorticotropic hormone]) leads to resolution of spasms faster and in more infants that does vigabatrin.
- Responses without subsequent relapse may be no different; that is, the percent of cases that remain seizure-free may be similar when recurrence of seizures is considered.
- There is a suggestion that prednisolone or tetracosactide (cosyntropin) might improve the long-term developmental outcomes compared to vigabatrin in infants not found to have an underlying cause of their infantile spasms.
- Vigabatrin may be the treatment of choice in infantile spasms related to tuberous sclerosis.
- The authors also noted that naturally occurring ACTH is not available in the U.K.

The Cochrane review summarizes data on the use of ACTH versus high-dose prednisolone that was part of one study by Lux in 2004; this component was nested within the comparison of vigabatrin with hormonal treatment. In this study, 19 of 25 patients (76%) treated with ACTH (40 to 60 U/alternate days) had cessation of spasms compared with 21 of 30 (70%) patients treated with prednisolone (40 to 60 mg/day); odds ratio: 1.36 (95% confidence interval: 0.41 to 4.53). The odds ratio for resolution of electroencephalogram (EEG) abnormalities in those for whom it was measured was 3.20 (favoring ACTH) and the confidence interval was 0.49 to 20.81.

A review article by Gettig and colleagues noted many of the same items as the Cochrane review. (4) They note that the effect of ACTH on long-term developmental outcomes in patients with infantile spasms warrants further research; the preferred dose and duration of treatment of infantile spasms with ACTH cannot be determined from the current evidence. They also comment that some of the poorly reported studies do not explicitly distinguish between ACTH and

cosyntropin, and it cannot be determined which treatment study patients received (natural vs. synthetic ACTH). They note that in some countries (e.g., Japan) cosyntropin is used interchangeably with ACTH because of access issues. This review provided information on 2 large surveys performed by Child Neurology Societies in the U.S. and Japan. In the U.S. survey reported in 1994, 88% of respondents used ACTH as initial therapy for infantile spasms with a dosage of 40 IU/day for 1 to 2 months and the choice of drug was not influenced by etiology. In the survey from Japan reported in 2000, treatment was influenced by etiology, and the order of drug selection was pyridoxine, valproate, and synthetic ACTH. In a smaller survey in the U.K. (1996), the initial choice was influenced by etiology, and vigabatrin was most frequently used for initial therapy. In addition, this review also comments that cosyntropin (synthetic ACTH) may be preferred over ACTH in diagnosing adrenal insufficiency because cosyntropin takes significantly less time (less than 1 hour compared to overnight).

Other potential uses of repository corticotrophin injection

Gout

Underwood (5) conducted a systematic review examining the effectiveness of treatments for acute gout. The author concluded that repository corticotropin injection may be equally effective as corticosteroids at reducing symptoms in patients with acute gout. The evidence included 1 randomized controlled trial (RCT) (n=31) of repository corticotropin injection versus a corticosteroid. The study did not include adverse events (harms). This evidence was given a low-quality rating by the authors.

Janssens et al. authored a Cochrane Review (6) that examined the efficacy and safety of systemic corticosteroids in the treatment of acute gout in comparison with placebo, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, other active drugs, other therapies including repository corticotropin injection, or no therapy. Clinically relevant differences between the studied systemic corticosteroids and the comparator drugs were not found; important safety problems attributable to the used corticosteroids were not reported. The quality of the 3 studies identified was graded as very low to moderate. Statistical pooling of results was not possible. The authors concluded that “There is inconclusive evidence for the efficacy and effectiveness of systemic corticosteroids in the treatment of acute gout.”

A review article by Schlesinger (7) discusses treatments for acute gout, emphasizing the use of repository corticotropin injection. The author notes that there are no formal guidelines for the treatment of acute gout and only a few RCTs have been conducted to evaluate the efficacy of the various treatments for acute gout. New research suggests that repository corticotropin injection acts peripherally by activation of the melanocortin type 3 receptor, and this could be responsible, at least in part, for its efficacy in acute gout. The author concludes that “Randomized, long term, prospective, placebo-controlled trials are needed to evaluate the therapeutic role of repository corticotropin injection versus NSAIDs (non steroidal anti-inflammatory drugs) and other treatment modalities, such as corticosteroids, in the treatment of acute gout.” Thus, some may not consider gout as a corticosteroid-responsive disease and may consider the use of repository corticotropin.

Childhood Epilepsy

Gayatri et al. authored a Cochrane review (8) to determine the efficacy of corticosteroids and repository corticotropin injection in terms of seizure control, improvements in cognition, quality of

life, and tolerability compared to placebo or other antiepileptic drugs for the treatment of childhood epilepsy. (This report was on childhood epilepsy other than epileptic spasms.) All RCTs of administration of corticosteroids or repository corticotropin injection to children (younger than 16 years) with epilepsy were included. Outcomes included cessation of seizures, reduction in seizure frequency, improvement in cognition, quality of life, and adverse effects. A single RCT was included that recruited 5 patients in a double-blind crossover trial. The authors concluded that "No evidence was found for the efficacy or safety of corticosteroids or repository corticotropin injection in treating childhood epilepsies. Clinicians using steroids in childhood epilepsies, other than for epileptic spasms, should take this into account before using these agents."

Tobacco Cessation
For potential use in tobacco cessation, one article described an uncontrolled study of its use in 15 patients. (9)

Nephrotic Syndrome
Bomback and colleagues published a retrospective case series including all known patients treated with adrenocorticotropic hormone (ACTH) gel for idiopathic, nondiabetic nephritic syndrome in the United States outside of research settings through 2009; patients needed to have been treated for at least 6 months. (10) Patients were identified by contacting nephrologists referred to the researchers by Questor Pharmaceuticals. A total of 25 patients were identified; data were not available for 4 patients. Of the 21 remaining patients, ACTH gel was used as a primary therapy in 3; the other 18 patients had failed a mean of 2.3 immunosuppressive regimens before using ACTH gel. An additional 5 patients were identified who were treated for less than 6 months and were taken off therapy for lack of response; these patients were not included in the analysis. Four of the 21 (19%) patients were in complete remission, defined as stable or improved renal function with final proteinuria falling to less than 500 mg/day. An additional 7 of 21 (33%) patients had a partial remission (at least a 50% reduction in proteinuria and final proteinuria 500 to 3,500 mg/day). The study was retrospective, had a small sample size, did not have a control group, and patient selection may have been biased.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 3 physician specialty societies and 1 academic medical center in April 2010. In addition, unsolicited input was received from 1 foundation and 3 physicians. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was strong support for use of repository corticotropin in treatment of infantile spasms (West Syndrome).

Summary

While questions still exist about the role of repository corticotropin in the treatment of infantile spasms, this has been accepted as a treatment option, and there is strong clinical support for this treatment. Thus, this use may be considered medically necessary. The evidence is insufficient to support the use of repository corticotropin injection in conditions not responsive to corticosteroid therapy (such as tobacco cessation, acute gout, childhood epilepsy) to improve the net health

outcome. Repository corticotropin injection is considered not medically necessary for patients with these conditions because the clinical outcomes with use of this specific material have not been shown to be superior to other approaches, including synthetic ACTH (cosyntropin), yet repository corticotropin is generally more costly than these alternatives. In addition, use of repository corticotropin may be associated with more adverse effects.

Practice Guidelines and Position Statements
In May 2004, the American Academy of Neurology; Child Neurology Society released *Practice Parameter: Medical Treatment of Infantile Spasms: Report of the American Academy of Neurology and the Child Neurology Society.* (2) The report states the following recommendations for adrenocorticotropin (ACTH): "ACTH is probably effective for the short-term treatment of infantile spasms and in the resolution of hypsarrhythmia. There is insufficient evidence to recommend the optimum dosage and duration of treatment with ACTH for the treatment of infantile spasms."

In 2010, an industry-sponsored Infantile Spasms Working Group published a consensus report on diagnosis and treatment of infantile spasms. (11) Regarding treatment, the report concluded: "At this time, ACTH and VGB (*vigabatrin*) are the only drugs with proven efficacy to suppress clinical spasms and abolish the hyparrhythmic EEG in a randomized clinical trial setting (Mackay et al., 2004) and thus remain first-line treatment."

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS
J0800 Injection, corticotropin, up to 40 units

REVISIONS

07-01-2012	Policy added to the bcbsks.com web site.
05-22-2013	Policy Title revised from "H.P. Acthar Gel (repository corticotropin) Prior Authorization Criteria" to "H.P. Acthar Gel (repository corticotropin)"
	▪ Added links for Prior Authorization Form, Link to Drug List (Formulary), and For information concerning Prior Authorization Prescription Drugs. ▪ Added under Prior Authorization Form link "BCBSKS will review Prior Authorization requests effective May xx, 2013."
	Description section updated
	In Policy section: ▪ Revised policy statement from: "H.P. Acthar Gel will be approved: 1. when the patient has been diagnosed with Infantile spasms AND 2. the patient is < 24 months of age"

	To: "A. Repository corticotropin injection may be considered medically necessary for treatment of infantile spasms (West syndrome), when the patient is < 24 months of age. B. Use of repository corticotropin injection is considered not medically necessary as treatment of corticosteroid-responsive conditions, except when: 1. There are medical contraindications or intolerance to corticosteroids that are not also expected to occur with use of repository corticotropin injection. As reflected in the description section this may include, but not be limited to: Multiple Sclerosis, Rheumatic disorders, Collagen diseases, Dermatologic diseases, Allergic states, Ophthalmic diseases, Respiratory diseases, or Edematous state. OR 2. There has been an incomplete response to an adequate trial of corticosteroids. C. Repository corticotropin injection is considered not medically necessary for use in diagnostic testing of adrenocortical function. D. Except as noted here, use of repository corticotropin injection is considered experimental / investigational for conditions that are not responsive to corticosteroid therapy including, but not limited to, use in tobacco cessation, acute gout, and childhood epilepsy." ▪ Added Policy Guidelines ▪ Removed Dosing chart as dosing guidelines are referenced in Policy Guidelines
	Rationale section updated
	Added Coding section to include HCPCS code: J0800
	References updated

REFERENCES

1. H.P. Acthar Gel product labeling. Available online at: http://www.acthar.com/sites/all/themes/acthar/pdfs/Acthar-PI.pdf . Issued October 2010. Last accessed April 2012.
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4. Gettig J, Cummings JP, Matuszewski K. H.P. Acthar gel and cosyntropin review. P T 2009; 34(5):250-7.
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8. Gayatri NA, Ferrie CD, Cross H. Corticosteroids including ACTH for childhood epilepsy other than epileptic spasms. Cochrane Database Syst Rev 2007; (1):CD005222.
9. McElhaney JL. Repository corticotropin injection as an adjunct to smoking cessation during the initial nicotine withdrawal period: results from a family practice clinic. Clin Ther 1989; 11(6):846-53.