5.01.12 Repository Corticotropin Injection

Medical Policy

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Policy Date</th>
<th>Last Review Status/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription Drug</td>
<td>12:2013</td>
<td>Reviewed with literature search/12:2013</td>
</tr>
</tbody>
</table>

Issue
12:2013

Return to Medical Policy Index

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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 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, congestive 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 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 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**

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.

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**Policy**

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

Repository corticotropin injection may be considered **medically necessary** for treatment of infantile spasms (West’s syndrome) when a more cost-effective alternative has been tried and failed.
Use of repository corticotropin injection is considered **not medically necessary** as treatment of corticosteroid-responsive conditions, unless there are medical contraindications or intolerance to corticosteroids that are not also expected to occur with use of repository corticotropin injection.

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

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**Policy Guidelines**

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

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.

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**Rationale**

This policy was originally created in 2008 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period December 2009 through March 2011. Following is a summary of the key literature to date:

**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 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, tetrocosacride (synthetic ACTH [cosyntropin]) and ACTH) 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 tetrocosacride (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 (confidence interval 0.41 to 4.53). The odds ratio for resolution of 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. They note that the effect of ACTH on long-term developmental outcomes in patients with infantile spasms warrants further research; and that 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 two large surveys performed by Child Neurology Societies in the U.S. and Japan. In the US 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 et al. (5) conducted a systematic review examining the effectiveness of treatments for acute gout. The authors 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 (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 three 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 randomized controlled trials (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 (nonsteroidal 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 randomized controlled trials 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 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 obtained 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 or 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 3500 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 while this policy was under review for 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’s 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. (See Benefit Application section for contractual items that may impact use in this condition.) In addition, use of repository corticotropin may be associated with more adverse effects.

Guidelines, Recommendations 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 hypsarrythymia. 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.”

Medicare National Coverage
No national coverage determination

References:


<table>
<thead>
<tr>
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<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
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<td>96372</td>
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<td>Other generalized epilepsy and epileptic syndromes, not intractable code range</td>
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<td>ICD-10-PCS codes are only used for inpatient services. There is no specific code for this procedure</td>
</tr>
</tbody>
</table>

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Index

ACTH Gel
Adrenocorticotropin hormone (ACTH)
HP Acthar Gel