Abbreviated Drug Evaluation: Repository corticotropin injection

Month/Year of Review: March 2013
Generic Name: Repository corticotropin injection
PDL Class: None

End date of literature search: February 2013
Brand Name (Manufacturer): Acthar Gel® (Questcor Pharmaceuticals)
Dossier Received: Yes

FDA Approved Indication:
Repository corticotropin is an injectable formulation of the adrenocorticotropic hormone (ACTH) analogue indicated as monotherapy for the treatment of infantile spasms in infants and children less than 2 years of age and for the treatment of exacerbations of multiple sclerosis (MS) in adults. It may also be used for the following disorders that are corticosteroid responsive: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state.

Conclusions:
- 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)

Recommendations:
- Prior authorize repository corticotropin injection to allow coverage for the treatment of infantile spasms in patients less than 2 years of age and restrict other use for those who cannot tolerate appropriate glucocorticoid therapy.
Acthar Gel® is an injectable formulation (IM or SQ) of ACTH. It works by stimulating the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a few other androgenic substances. The three most common indications of ACTH are adrenocortical testing, MS, and infantile spasms (West syndrome). ACTH was originally approved in 1952 for a broad range of corticosteroid-responsive conditions in which systemic corticosteroids (prednisone) are commonly used today. Currently, these labeled indications include rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmologic diseases, respiratory diseases, and edematous states. Previously, cosyntropin was available only as the brand-name product Cortrosyn® which is indicated for diagnostic testing of adrenal function. Cosyntropin products have been used off-label to treat a variety of diseases. In 2008, Questcor implemented a new strategy for Acthar Gel®, including a price increase to continue manufacturing and distributing this agent.

Infantile spasms, or West syndrome, is a rare disorder that includes a type of epileptic seizure and an electroencephalogram (EEG) finding called hypsarrhythmia. Onset usually occurs before age of one. While the seizures generally resolve by the age of 3, long-term prognosis is poor, with a high incidence of developmental delay, structural neurological abnormalities and persistent seizure activity. The goal of infantile spasms treatment is to stop the seizures, normalize the EEG, and optimize the neurodevelopmental outcome. The FDA approved repository corticotropin injection for the treatment of infantile spasms in 2010. FDA approval was based on one randomized controlled trial and one supportive trial demonstrating efficacy in the cessation of spasms and amelioration of the EEG, not in the prevention of other seizure types, improvement in long-term developmental outcomes, or any other outcomes. Approval was based on a re-analysis of data from previously published studies. No prospectively designed statistical analysis was performed. Other treatment options are corticosteroids, including prednisone, prednisolone, and methylprednisolone, and vigabatrin. The optimum dose and duration of treatment has not sufficiently been defined by the evidence for ACTH. However, short duration of approximately 2 weeks followed by a taper is preferred. The most frequent adverse effects associated with short term use include irritability, increased appetite leading to weight gain, and Cushingoid features.

According to the FDA medical reviewer, the combined endpoint of elimination of spasms and hypsarrhythmia is generally recognized as the most clinically meaningful endpoint for efficacy studies of infantile spasms. For studies with a mean follow-up of at least 12 months, intermediate to long-term outcome measures are EEG without epileptiform abnormalities, absence of seizures, and normal development.

For the treatment of exacerbations of multiple sclerosis (MS), both ACTH and corticosteroids have been used. They reduce inflammatory response by inducing several effects on the immune system. There is limited evidence on effect on outcomes from treating exacerbations and no randomized controlled trials (RCTs) are currently available. The goal in the treatment of MS exacerbations is to reduce short term disability after an exacerbation, prevent new exacerbations, and reduce long term disability. Acute attacks are usually treated with glucocorticoids, such as a 3 to 7 day course of intravenous methylprednisolone. This may sometimes be followed by a tapered dose of oral steroids. Repository corticotropin is typically used in patients who cannot tolerate high-dose glucocorticoids. There is insufficient evidence demonstrating a difference in rate of recovery between high dose glucocorticoids and ACTH in the treatment of MS exacerbations. The most effective dose and duration of repository corticotropin injection have not been determined and a dose of 80 units/day for at least 5 days and for as many as 15 days is commonly used.

Overall, there is a lack of studies comparing the effectiveness of repository corticotropin to corticosteroids in corticosteroid-responsive conditions. There is no reliable evidence in persons who have failed to respond to first line corticosteroids. There remains uncertainties concerning the effect of repository corticotropin on the magnitude of endogenous cortisol production and therefore has a potential for significant adverse effects. Although previously used as an
aid in the diagnosis of adrenocortical insufficiency, this indication was removed from the repository corticotropin label in 2010. There is insufficient evidence to support its use.

Methods:
A Medline literature search ending February 2013 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) comparing repository corticotropin injection was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Efficacy Summary:
West Syndrome:
Corticotropin injection was FDA approved for infantile spasms in 2010 based on a 1996 single blinded clinical trial comparing a 2 week course of ACTH 75 u/m2 twice daily to prednisone 1 mg/kg twice daily in 29 infants under 2 years of age (n=29). The treating physician was not blinded to treatment assignment, but the EEGs were read by a blinded evaluator. The median age was slightly higher in the prednisone group compared to the ACTH group. The primary outcome was the number in each group who were treatment responders, defined as having a complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG. After treatment, 13 (86.7%) of those randomized to ACTH compared to 4 (28.6%) of those given prednisone responded (p=0.0015). The lack of double blinding and small nature of this study add risk of bias to the results and should be interpreted with caution. In addition, there was not a defined statistical plan and the primary outcomes were not chosen in advance by authors.

Systematic Reviews:
A 2008 systematic review from the Cochrane Collaboration compared the effects of therapies to treat infantile spasms in terms of control of spasms, resolution of hypersarrhythmia, long-term psychomotor development, and subsequent epilepsy rates. Fourteen RCT’s were included (n=667), evaluating 9 different medications. Overall, quality and methodology of the included RCT’s were poor. Most studies included small numbers of participants and blinding of recipients only occurred in four studies. No studies evaluated long-term psychomotor development. Twelve of the 14 studies had a high risk of bias. In addition, many of the studies did not explicitly distinguish between ACTH and cosyntropin and it cannot be determined which treatment study patients received. The authors concluded that no single treatment has been proven to be more efficacious in treating infantile spasms than any of the others. However, the strongest evidence suggests that hormonal treatment (ACTH) leads to resolution of spasms faster and in more infants than does vigabatrin.

One study included a nested analysis of ACTH versus high-dose prednisolone and found 19 or 25 patients (76%) treated with ACTH had cessation of spasms compared with 21 of 30 (70%) patients treated with prednisolone (OR 1.36, 95% CI 0.41-4.53). However, this was an analysis nested within the comparison of vigabatrin with hormonal treatment. Effects on reduction in spasms, time to relapse, and psychomotor development were not reported.
Clinical Guidelines

A 2004 practice parameter from the American Academy of Neurology concluded that repository corticotropin injection is probably an effective agent in the short-term treatment of infantile spasms. The guidelines also concluded that there is insufficient evidence to determine whether oral corticosteroids are effective, and that vigabatrin was possibly effective but there are significant concerns about retinal toxicity.

These practice guidelines were updated in 2012 through a literature search up to 2011. Main conclusions of the updated guidelines are as follows:

- Data is insufficient regarding the equivalence of other corticosteroids to ACTH as being effective for short-term treatment of infantile spasms (Level U recommendation based on non-randomized trials and consensus opinion). Data is inadequate or conflicting.
- Low dose ACTH is an alternative to high-dose ACTH based on Class I (RCT) evidence showing similar efficacy.
- ACTH or vigabatrin may be offered for short-term first line treatment of infantile spasms. However, evidence suggests that ACTH may be offered over vigabatrin (Level C recommendation; possibly effective) and may result in better long-term cognitive outcomes than vigabatrin.
- Insufficient evidence exists to support other antiepileptic drugs.

Multiple Sclerosis

Systematic Reviews:

A 2000 Cochrane review evaluated the efficacy and safety of corticosteroids or ACTH in reducing short term and long term morbidity associated with MS. Only six trials were identified for the evaluation and risk of bias was high. However, all trials did suggest a benefit of ACTH or high doses of methylprednisolone in improving acute exacerbation of symptoms within the first five weeks of treatment (OR 0.378, 95% CI 0.24-0.57). There was insufficient evidence to determine if steroids or ACTH treatment prevented new exacerbations or worsening of long-term disability. There was also insufficient evidence to support the use of one drug, methylprednisolone or ACTH, over the other. Indirect comparisons indicated that methylprednisolone may show a greater benefit compared to ACTH and that the intravenous administration may give greater effect than oral administration.

Randomized Controlled Trials

Since the systematic review, one small, prospective, open-label, poor quality trial compared a 5-day course of self-administered ACTH for exacerbations of MS. Of the 20 study patients, 19 completed the study and results suggested that a five-day course of patient administered ACTH gel therapy may relieve symptoms of acute exacerbations of MS. There were small, non-significant, differences favoring the intramuscular route compared to the subcutaneous route.

A small, open-label, pilot study comparing monthly pulse ACTH therapy added to beta interferon to methylprednisone has been completed. However, it has not been published and only the abstract is available.

Clinical Guidelines

2003 Guidance from NICE recommends that any individual who experiences an acute episode should be offered a course of high-dose corticosteroids. Recommendations include IV methylprednisolone, 500mg-1g daily, for between 3 and 5 days. An update of the clinical guidance is scheduled for 2013.

Guidelines from the American Academy of Neurology conclude that glucocorticoid treatment has been demonstrated to have a short-term benefit on the speed of functional recovery in acute attacks of MS. They give a Type A recommendation to consider treatment with glucocorticoids for any patient with an acute attack of MS.
Other Indications
For the treatment of corticosteroid-responsive conditions, no randomized clinical studies were found. Only retrospective case series or open-label studies were identified from the literature search. There is no quality evidence of the effectiveness of ACTH gel in those who have failed to respond to corticosteroids.

Nephrotic Syndrome:
The clinical practice guidelines for glomerulonephritis from the Kidney Disease Improving Global Outcomes (KDIGO) were updated in 2013. For the treatment of idiopathic membranous nephropathy, the guidelines state that there have been preliminary reports of uncontrolled studies demonstrating effects of ACTH in gel formulation. However, no RCT’s have been conducted with this formulation and no recommendations can be made for the use of ACTH for treatment. They also conclude there is insufficient evidence to use in the treatment of patients resistant to first-line therapy.

In a retrospective case series published in 2011, Bomback, et al. evaluated all known cases of idiopathic nephrotic syndrome treated with ACTH gel through prescription. Data in the United States was available for 21 patients. Three of these patients were using it as primary therapy while the remaining patients had failed previous immunosuppressive regimens. Overall 11 patients (52%) achieved a complete or partial remission and 4 (19%) achieved complete remission. Important limitations of this data include the observational study method, lack of randomization, lack of control, short follow-up, and small number of patients. No formal statistical analysis was able to be performed and therefore it is difficult to interpret these results.

On additional, open label, prospective, nonblinded study, evaluated the use of ACTH gel on 15 patients with resistant glomerular diseases (2012). Resistant disease was defined as failure to achieve sustained remission with at least 2 prior immunosuppressive regimens (idiopathic membranous nephropathy), failure to achieve remission with corticosteroids and at least 1 other immunosuppressive regimen (minimal change disease/focal segmental glomerulosclerosis), or resistant disease despite maximum tolerated doses of renin-angiotensin-aldosterone blockade (IGA nephropathy). Patients received ACTH gel 40 units subcutaneously twice weekly for 2 weeks, followed by 80 units twice weekly for 22 weeks. The primary outcome was remission status at the completion of ACTH therapy. Again, no formal statistical analysis was able to be completed due to the small number and pilot study design. Overall, 4 subjects achieved partial remission and 3 subjects discontinued therapy early due to adverse events. Two because of worsening glycemic control and one due to weight gain. The many limitations including small sample, lack of control group, short-term follow up, and lack of randomization make it difficult to interpret these results.

Dermatomyositis
A single retrospective case series provides clinical observations on treating patients with refractory dermatomyositis and polymyositis using ACTH gel. Patients observed had either failed or were unable to tolerate the side effects of previous therapy with steroids, intravenous immunoglobulins, and steroid-sparing drugs. The author reported that improvement in manual muscle testing at 3 months was seen in all patients, including improved muscle strength, decreased pain, and resolution of skin involvement but further studies are needed.
References:


Appendix 1: Specific Drug Information

DOSE & AVAILABILITY

<table>
<thead>
<tr>
<th>STRENGTH</th>
<th>ROUTE</th>
<th>FREQUENCY</th>
<th>DOSAGE:</th>
<th>RENAL ADJ</th>
<th>HEPATIC ADJ</th>
<th>Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 USP units per mL</td>
<td>IM or SubQ</td>
<td>Every 24-72 hours</td>
<td><strong>Infantile Spasms:</strong> 75 U/m2 twice daily. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period. <strong>Acute Exacerbations of MS:</strong> 80-120 units daily for 2-3 weeks. A taper may be necessary. In the treatment of other disorders and diseases, dosing needs to be individualized. The usual dose is 40-80 units IM or SubQ every 24-72 hours.</td>
<td>Has not been studied.</td>
<td>Has not been studied. Enhanced effect in liver cirrhosis.</td>
<td>Indicated for the treatment of infantile spasms in children age 2 and under.</td>
</tr>
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Other Dosing Considerations:

For the treatment of infantile spasms, the following is one suggested tapering schedule: 30 U/m2 in the morning for 3 days; 15 U/m2 in the morning for 3 days; 10 U/m2 in the morning for 3 days; and 10 U/m2 every other morning for 6 days.

Dosing is typically based on body surface area (BSA). For calculation of body surface area, use the following formulary:

\[ BSA(m^2) = \sqrt{\frac{weight (kg) \times height (cm)}{3600}} \]

For the treatment of MS, although drug dependence does not occur, sudden withdrawal after prolonged use may lead to adrenal insufficiency or recurrent symptoms which makes it difficult to stop the treatment. It may be necessary to taper the dose.

For other indications in those over 2 years of age, dosage should be individualized based on the disease and general medical condition of each patient. Frequency and dose should be determined by considering severity of the disease and the initial response of the patient.

DRUG SAFETY

*Serious (REMS, Black Box Warnings, Contraindications):*

*Contraindications:*
Patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin.

Administration of live or attenuated vaccines
Children under 2 years of age with suspected congenital infections.

Warnings and Precautions:
Infections – increased susceptibility to new infection and increased risk of exacerbation, dissemination or reactivation of latent infections.
Adrenal insufficiency after prolonged therapy
Cushing’s Syndrome
Elevated blood pressure, salt and water retention
Vaccination
Masking of symptoms of other underlying disease/disorders
GI perforation and bleeding
Behavioral and mood disturbances
Comorbid Diseases – symptoms of diabetes and myasthenia gravis may be worsened
Negative effects on growth and physical development
Appendix 2: Suggested PA Criteria

Repository Corticotropin Injection (Acthar Gel®)

Goal(s):
- To ensure appropriate drug use and limit to patient populations in which corticotropin has been shown to be effective and safe.

Length of Authorization: 4 weeks

<table>
<thead>
<tr>
<th>Approval Criteria</th>
<th>Yes: Approve up to 4 weeks (2 weeks of treatment, and 2 weeks of taper)</th>
<th>No: Go to #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the diagnosis?</td>
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<tr>
<td>2. Is the diagnosis monotherapy for infantile spasms in infants and children under 2 years of age (ICD-9 345.6)?</td>
<td>Yes: Approve up to 4 weeks (2 weeks of treatment, and 2 weeks of taper)</td>
<td>No: Go to #3</td>
</tr>
<tr>
<td>3. Is the diagnosis for acute exacerbation or relapse of multiple sclerosis (ICD-9 340)?</td>
<td>Yes: Go to #4.</td>
<td>No: Pass to RPH; Deny (medical appropriateness)</td>
</tr>
<tr>
<td>4. Has the patient tried and unable to tolerate IV methylprednisolone or oral administration of high-dose methylprednisolone?</td>
<td>Yes: Approve up to 5 weeks (3 weeks of treatment, followed by taper)</td>
<td>No: Go to #5</td>
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<tr>
<td>5. Is the prescription for adjunctive therapy for short term administration in corticosteroid-responsive conditions including</td>
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<td>- The following rheumatic disorders: psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis (ICD-9 696.0, 714, 714.3, 720.0, 710.0)? OR</td>
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<td>- The following collagen diseases: systemic lupus erythematosus, systemic deramatomyositis (ICD-9 710.0, 710.3, 710.4)?, OR</td>
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<td>- Dermatologic diseases such as erythema multiforme, Stevens-Johnson syndrome (ICD-9 695.1, 695.13, 695.14)?, OR</td>
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<tr>
<td>- Ophthalmic diseases such as keratitis, iritis, uveitis, optic neuritis, or chorioretinitis (ICD-9 970, 364.0-364.3, 377.3, 363.2)?, OR</td>
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<tr>
<td>- For the treatment of respiratory diseases including Symptomatic Sarcoidosis (ICD-9</td>
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<tr>
<td>- For treatment of an edematous state (ICD-9 782.3)?</td>
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<tr>
<td>6. Are there contraindications or intolerance to any, or therapeutic failure with at least one intravenous corticosteroid?</td>
<td>Yes: Approve x 6 months</td>
<td>No: Pass to RPH; Deny (medical appropriateness)</td>
</tr>
</tbody>
</table>

Note: RPH stands for Retail Pharmacy Hotline.
**Dosing:**

**Infantile spasms in children under 2 years of age**
- Must be administered intramuscularly
- 75 U/m² twice daily over a 2 week period
- Dose should then be tapered over a 2 week period to avoid adrenal insufficiency

**Acute exacerbations of multiple sclerosis in adults**
- May be given intramuscularly or subcutaneously
- 80-120 U daily for 2-3 weeks
- It may be necessary to taper the dose

**Other indications for adults and children over 2 years of age**
- Dosage should be individualized according to the disease under treatment and the general medical condition of each patient.
- The usual dose is 40-80 U every 24-72 hours

_DUR Board Action: 5-30-2013 (MH)_
Revision(s):
Initiated: