For patients with proteinuria due to nephrotic syndrome who were previously treated with first-line therapy

Consider Acthar Gel for Post-transplant FSGS

Indication
Acthar® Gel (repository corticotropin injection) is indicated to induce a diuresis or a remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

SELECT IMPORTANT SAFETY INFORMATION

Contraindications
- Acthar should never be administered intravenously
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar
- Acthar is contraindicated where congenital infections are suspected in infants
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction, or sensitivity to proteins of porcine origin

Please see additional Important Safety Information throughout and on page 10. Please see accompanying full Prescribing Information.
Post-transplant FSGS is a serious concern

Prevalence and progression of FSGS

<table>
<thead>
<tr>
<th>Prevalence in patients with FSGS(^5) (native kidney)</th>
<th>Relapse rate(^4) (native kidney)</th>
<th>Rate of progression to ESRD(^3) (native kidney)</th>
<th>Recurrence in post-renal transplantation(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>43%</td>
<td>40%</td>
<td>Up to 60%</td>
<td>Overall 20%-50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May exceed 80% with history of graft loss</td>
</tr>
</tbody>
</table>

• Transplant recipients with recurrent FSGS are more likely to experience renal complications compared with those with no recurrence\(^4,5\)

Risk factors may predict greater risk of FSGS recurrence in renal grafts\(^6,7\)

- Non-black race
- Severe proteinuria
- Rapid progression in native kidneys (<3 years from diagnosis)
- Prior history of graft loss secondary to disease recurrence
- Initial sensitivity to steroids

ESRD=end-stage renal disease; FSGS=focal segmental glomerulosclerosis.

Reduction of proteinuria to remission levels is an important goal in NS

Proteinuria is an important marker of glomerulonephropathies commonly seen in FSGS\(^2\)

- Proteinuria is a critical, modifiable risk factor to slow progression of disease\(^8,9\)
- Reduction of urine protein excretion should be the main goal of treatment\(^8,9\)

Study included 281 patients with primary FSGS from the Canadian Glomerulonephritis Registry. Patients had baseline proteinuria of 4.7 g/day and had nephrotic-range proteinuria at some point during the ≥12 months of follow-up.\(^10\)

Complete remission: proteinuria ≤300 mg/day; partial remission: proteinuria <3500 mg/day plus a >50% reduction from peak value.\(^2\)

CR=complete remission; NR=no remission; NS=nephrotic syndrome; PR=partial remission.
Podocytes are exposed to circulating factors that penetrate the endothelium and glomerular basement membrane (GBM) layers. Excessive levels of circulating factors have been associated with podocyte injury and dysfunction of the glomerular filtration barrier.

Management of recurrent FSGS remains a significant problem among post-transplant patients. There is a lack of a standardized protocol for the management of proteinuria following transplant. Evidence-based treatment options are limited, and current options are supported by data from small studies and case reports.

Conventional approaches to post-transplant FSGS treatment involve different therapeutic mechanisms:
- Therapeutic plasma exchange (TPE)
- Glucocorticoids
- Calcineurin inhibitors (CNI)
- Chemotherapy and immunosuppressants
- Renin-angiotensin system blocker
- Anti-CD20 mAB
- T-cell costimulation modulator

Second-line treatment
Standardized approach remains unclear.
Acthar Gel is believed to work via a different pathway by binding to receptors on podocytes and immune cells.

While the exact mechanism of action of Acthar Gel is not fully understood, further investigation is being conducted. This information is based on nonclinical data, and the relationship to clinical benefit is unknown.

Induces cortisol production at levels slightly above endogenous range\(^20,21\)
- Normal endogenous secretion of corticosteroid is equivalent to 5 to 7.5 mg of prednisone\(^22\)
- In PD studies, the cortisol exposure after 5 doses of Acthar Gel 80 units 2 times per week was equivalent to 8.83 mg of prednisone daily, which is 1.3 mg above the normal endogenous range\(^20,22,23\)

Low cortisol exposure indicates Acthar Gel may work through another mechanism, independent of its effect on the adrenal gland\(^24\)

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions
- The adverse effects of Acthar are related primarily to its steroidogenic effects
- Acthar may increase susceptibility to new infection or reactivation of latent infections

Please see accompanying full Prescribing Information.

Potential Mechanism of Action

Binds directly to receptors on podocytes
- Stabilizing synaptopodin, a podocyte-specific protein that helps maintain the structure of the podocyte actin cytoskeleton\(^14,17,18\)
- Reducing podocyte foot process effacement and podocyte apoptosis\(^14,17,18\)
- Improving histologic signs of renal injury\(^14\)
- Reducing glomerular permeability\(^14,18\)
- Restoring the balance of immune cell populations\(^18\)

Direct Effects on Podocytes in the Kidney
- Reducing podocyte foot process effacement and podocyte apoptosis\(^14,17,18\)
- Stabilizing synaptopodin, a podocyte-specific protein that helps maintain the structure of the podocyte actin cytoskeleton\(^14,17,18\)
- Improving histologic signs of renal injury\(^14\)
- Reducing glomerular permeability\(^14,18\)
- Restoring the balance of immune cell populations\(^18\)

Modulation of the Immune Response
- Downregulating proinflammatory response pathways to diminish expression of inflammatory mediators implicated in the immune response\(^2,9,26\)
- Regulating autoantibody production by modulating hyperactive T and B lymphocytes\(^18\)
- RESTORING THE BALANCE OF IMMUNE CELL POPULATIONS\(^18\)

Body of Evidence

Clinical parameters that helped characterize patients with FSGS included severity of proteinuria, renal impairment, and previous IST\(^4,25-33,35\)

<table>
<thead>
<tr>
<th>Patients with nephrotic-range proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal impairment</strong></td>
</tr>
<tr>
<td>Received ≥1 prior treatment</td>
</tr>
</tbody>
</table>

| Native kidney FSGS\(^1)\) (n=62) | Post-transplant FSGS\(^1)\) (n=34) |
|------------------------------------------|
| **Renal impairment** | **Serum creatinine:** study average from 2.4 mg/dL to 3.3 mg/dL | **eGFR:** study average from 30.7 mL/min/1.73 m\(^2\) to 36.5 mL/min/1.73 m\(^2\) |
| Received ≥1 prior treatment | 100% had ≥1 previous IST | 74% received TPE +/- rituximab |

\(^1\)Previous IST may have included all of the following: steroids, CNI, MMF, CTX, cyclosporine, tacrolimus, rapamycin, abatacept, chlorambucil, methotrexate, ciclosporine, and/or rituximab. Other than steroids, listed therapies are not approved for the reduction of proteinuria in NS.
Clinical data of Acthar Gel in post-transplant FSGS

Newest data on Acthar Gel for the treatment of proteinuria in patients with post-transplant FSGS—clinical experience from Georgetown-Howard Universities Center for Clinical and Translational Science and Indiana University School of Medicine\(^{12}\)

Overview\(^{12}\)
- Retrospective case-review study of Acthar Gel in kidney transplant patients (N=14) with biopsy-confirmed post-transplant recurrent FSGS
- Before the use of Acthar Gel, the majority of patients were treated with plasmapheresis (71%) 

Patient characteristics

<table>
<thead>
<tr>
<th>Treatment outcome definitions from Grafals et al, 2019 publication</th>
<th>Post hoc analysis outcome(^{2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>21% (3/14)</td>
</tr>
<tr>
<td>Partial</td>
<td>15% (2/14)</td>
</tr>
<tr>
<td>Remission</td>
<td>36% (5/14)</td>
</tr>
<tr>
<td>Complete</td>
<td>25% (7/14)</td>
</tr>
<tr>
<td>Partial</td>
<td>14% (2/14)</td>
</tr>
<tr>
<td>Remission</td>
<td>50% (7/14)</td>
</tr>
<tr>
<td>Complete</td>
<td>21% (3/14)</td>
</tr>
<tr>
<td>Partial</td>
<td>21% (3/14)</td>
</tr>
</tbody>
</table>

Change in proteinuria following Acthar Gel treatment\(^{10}\)

<table>
<thead>
<tr>
<th>UPCR before treatment</th>
<th>UPCR after treatment</th>
<th>Percentage reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Acthar Gel (N=14)</td>
<td>7.3 g/g</td>
<td></td>
</tr>
<tr>
<td>Post-Acthar Gel (n=13)</td>
<td>3.6 g/g</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\)Calculation based on patients who had reported pre- and post-Acthar Gel values (adapted from Table 3: Acthar Gel Treatment Outcome). Does not include 1 patient who discontinued treatment due to ESRD. 

**SELECT IMPORTANT SAFETY INFORMATION**

Warnings and Precautions (cont.)
- Suppression of the hypothalamic-pituitary-adrenal (HPA) axis may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA suppression after stopping treatment.
- Cushing’s syndrome may occur during therapy but generally resolves after therapy is stopped. Monitor patients for signs and symptoms.
- Acthar can cause elevation of blood pressure, salt and water retention, and hypokalemia. Blood pressure, sodium, and potassium levels may need to be monitored.
- Acthar often acts by masking symptoms of other diseases/disorders. Monitor patients carefully during and for a period following discontinuation of therapy.
Other observations reported for patients with post-transplant FSGS

Changes in renal function following Acthar Gel therapy in post-transplant FSGS patients

<table>
<thead>
<tr>
<th>Response type</th>
<th>Pre-Acthar Gel</th>
<th>Post-Acthar Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SCR</td>
<td>2.4 mg/dL (n=14)</td>
<td>2.2 mg/dL (n=14)*</td>
</tr>
<tr>
<td>Mean eGFR</td>
<td>36.5 mL/min/1.73 m² (n=13)*</td>
<td>45.2 mL/min/1.73 m² (n=13)*</td>
</tr>
</tbody>
</table>

*Calculated based on patients who had reported pre- and post-Acthar Gel values (adapted from Table 3: Acthar Gel Treatment Outcome).
†1 patient with eGFR <10 mL/min/1.73 m² at baseline was excluded from the analysis.
‡3 patients with ESRD were excluded from the analysis.

Safety findings in post-transplant patients with FSGS

- Adverse events (AEs) were reported by 29% (4/14) of patients receiving Acthar Gel treatment, including swelling or edema (2/14), tiredness or fatigue (1/14), diabetes (1/14), hyperglycemia (1/14), and weight gain (1/14).
- No patients discontinued Acthar Gel treatment due to side effects.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont.)

- Acthar can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Monitor for signs of bleeding.
- Acthar may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changes, and severe depression to psychosis. Existing conditions may be aggravated.
- Patients with comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar in patients with diabetes and myasthenia gravis.
- Prolonged use of Acthar may produce cataracts, glaucoma, and secondary ocular infections. Monitor for signs and symptoms.
- Acthar is immunogenic and prolonged administration of Acthar may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH activity.
- There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver.

Clinical data of Acthar Gel in post-transplant FSGS

Largest retrospective dataset on Acthar Gel for the treatment of proteinuria in patients with post-transplant FSGS—clinical experience from Washington University and Johns Hopkins University

Overview

- Retrospective case review of Acthar Gel in kidney transplant recipients (N=20) with de novo or recurrent FSGS resistant to TPE and rituximab.
- Majority of patients were previously treated with first-line therapy of TPE and/or rituximab for post-transplant FSGS.

Patient characteristics

- Mean baseline proteinuria: 8.6 ± 7.6 g/g
- Mean baseline eGFR: 30.7 ± 19.3 mL/min/1.73 m²
- Mean baseline serum creatinine: 3.3 ± 2.7 mg/dL
- Median (IQR) time to post-transplant FSGS recurrence: 3 months (0.75-7.5 months)
- Time from diagnosis to ESRD in native kidney: Median 3 years (IQR: 1-5 years)
- Prior kidney transplant: 8 patients (7 of 8 had history of FSGS)

Treatment history (study center protocol)

- Before the use of Acthar, the majority of patients with post-transplant FSGS were treated with TPE (75%) or TPE plus rituximab (50%).

Study dosing

The majority of patients (11/20) in this study received Acthar Gel 80 units subcutaneously, twice weekly for at least 6 months.

- The usual dose of Acthar Gel is 40-80 units given intramuscularly or subcutaneously every 24-72 hours.
- In Acthar Gel clinical datasets, the most common Acthar Gel dosing regimen was 80 units subcutaneously twice weekly for 6 months.
Post-transplant patients taking Acthar Gel experienced a reduction in proteinuria to remission levels

**Significant reduction in proteinuria (N=20)**

<table>
<thead>
<tr>
<th>Pre-Acthar Gel</th>
<th>Post-Acthar Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPCR (g/g)</td>
<td>Mean serum creatinine (mg/dL)</td>
</tr>
<tr>
<td>8.6 ± 7.6 g/g</td>
<td>3.3 ± 2.7</td>
</tr>
<tr>
<td>3.3 ± 2.3 g/g</td>
<td>2.8 ± 1.67</td>
</tr>
</tbody>
</table>

*62% reduction in mean proteinuria P=0.004

**Stable renal function was observed following Acthar Gel therapy**

- **50% (10/20) achieved remission**
- **20% (4/20) complete remission**
- **30% (6/20) partial remission**

3 of 4 patients with collapsing FSGS achieved remission (1 CR, 2 PR)

All 4 patients experienced a reduction in proteinuria

**Other observations reported for patients with post-transplant FSGS**

**Graft status (2012-2016 observation period)**

<table>
<thead>
<tr>
<th>Response type</th>
<th>N</th>
<th>No reported graft failure</th>
<th>Reported graft failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Partial remission</td>
<td>6</td>
<td>4</td>
<td>2^</td>
</tr>
<tr>
<td>No response</td>
<td>10</td>
<td>4</td>
<td>6^</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

**Therapeutic plasma exchange (TPE)**

| TPE utilization | 6 of 10 reported discontinued TPE | 4 of 10 reported less frequent use of TPE |

*Graft failure reported 27 and 36 months after completion of Acthar Gel treatment.

**SELECT IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions (cont.)**

- Long-term use may have negative effects on growth and physical development in children. Monitor pediatric patients
- Decrease in bone density may occur. Bone density should be monitored for patients on long-term therapy
- Pregnancy Class C: Acthar has been shown to have an embryocidal effect and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

**Adverse Reactions**

- Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain
- Specific adverse reactions reported in IS clinical trials in infants and children under 2 years of age included: infection, hypertension, irritability, Cushimgoid symptoms, constipation, diarhoea, vomiting, pyrexia, weight gain, increased appetite, decreased appetite, nasal congestion, acne, rash, and cardiac hypertrophy. Convulsions were also reported, but these may actually be occurring because some IS patients progress to other forms of seizures and IS sometimes masks other seizures, which become visible once the clinical spasms from IS resolve

Other adverse events reported are included in the accompanying full Prescribing Information.
In previously treated patients with FSGS in the native kidney
Patients experienced a significant reduction in proteinuria following Acthar Gel treatment

47% of patients (7/15) achieved partial remission defined as reduction in proteinuria with stable or improved renal function in a post hoc analysis*†26,38

Overview

Results are from a multicenter, retrospective case series of adult patients with various etiologies of NS (N=44), 15 of whom had FSGS. Patients received Acthar Gel 80 units twice weekly for at least 6 months. Presentation of study design, baseline characteristics, efficacy, and safety findings are based on content from Madan et al, 2016, where proteinuria reduction was evaluated as a treatment outcome. Impact on renal function as part of the outcome definition was not reported for the entire population.

A post hoc analysis was then conducted by Mallinckrodt that assessed treatment response to Acthar Gel based on a compound primary outcome measure that included both reduction in proteinuria and preserved or improved renal function (creatinine ≤25% of baseline or eGFR ≥75% of baseline). This compound outcome measure aligns with the KDIGO guidelines recommendations for assessing treatment response to NS therapy.

Study limitations

Results are based on a retrospective case series of 44 patients and may not be fully representative of outcomes in the overall patient population. While this review includes a diverse set of NS etiologies, a significant limitation is small patient numbers in several of the etiology subgroups and a retrospective design without a control group. Because initiation of treatment was based on the judgment of the treating clinician, excluding the IgAN group, 8 patients began treatment at a non-nephrotic proteinuria level >3500 mg/day. Most patients were on multiple therapies. The clinical outcomes may not be solely attributable to Acthar Gel. Longer treatment duration and follow-up may be needed for meaningful treatment responses. The relapse rate following successful treatment with Acthar Gel is not yet known.

Please see additional Important Safety Information throughout and on page 10. Please see accompanying full Prescribing Information.
Calculation based on patients who had reported pre- and post-Acthar Gel values (adapted from Table 2: Response to Acthar Gel). Does not include 1 patient who terminated early due to ESRD.

Please see accompanying full Prescribing Information. Please see additional Important Safety Information throughout and on page 10.

• Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction, or sensitivity to proteins of porcine origin. Contraindications (cont.)

SELECT IMPORTANT SAFETY INFORMATION

Contraindications (cont.)

- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction, or sensitivity to proteins of porcine origin.

Please see additional Important Safety Information throughout and on page 10. Please see accompanying full Prescribing Information.

In patients with clinically advanced FSGS, including those with collapsing lesions

Patients taking Acthar Gel experienced a reduction in proteinuria to remission levels

40% of patients (4/10) treated with Acthar Gel achieved remission defined as proteinuria reduction with stable renal function

Overview

Results are from a retrospective case series of 13 patients, 10 of whom had FSGS. Nine of 10 FSGS patients received Acthar Gel 80 units twice weekly for a duration of 1-10 months, with the exception of 1 patient who was on ongoing treatment.

Patient characteristics

Baseline proteinuria

3100-36,000 mg/g; 5.8-8.4 g/day

Mean baseline serum creatinine

2.22 mg/dL

FSGS variants

Collapsing (n=3)
TIP (n=1)
Not otherwise specified (n=2)
Not further categorized (n=4)

Results

40% (4/10) achieved remission: defined as proteinuria reduction with stable renal function

20% (2/10) complete remission
20% (2/10) partial remission

2 of 3 patients with collapsing FSGS achieved remission (Columbia, 1998)
All 3 patients experienced a reduction in proteinuria

Renal function

Mean serum creatinine

Baseline 2.22 mg/dL
Post-Acthar Gel 212 mg/dL

40% of patients (4/10) treated with Acthar Gel achieved remission defined as proteinuria reduction with stable renal function

Overview

Results are from a retrospective observational data and prospective data of patients who were not randomly assigned to therapy. There was no comparison group for interpretation of safety and efficacy findings with Acthar Gel. Most patients were on multiple therapies during Acthar Gel treatment, and the clinical outcomes may not be solely attributable to Acthar Gel. Acthar Gel dosing regimens and duration varied, and these limitations should be taken into consideration when interpreting the results.

Study limitations

The results may not be fully representative of outcomes in the overall patient population. Results are based on retrospective observational data and prospective data of patients who were not randomly assigned to therapy. There was no comparison group for interpretation of safety and efficacy findings with Acthar Gel. Most patients were on multiple therapies during Acthar Gel treatment, and the clinical outcomes may not be solely attributable to Acthar Gel. Acthar Gel dosing regimens and duration varied, and these limitations should be taken into consideration when interpreting the results.

Study limitations
Across multiple datasets of patients with FSGS in the native kidney

Adverse events were consistent with Acthar Gel’s established safety and tolerability profile

<table>
<thead>
<tr>
<th>Type of dataset</th>
<th>Retrospective case series (n=15)†</th>
<th>Prospective, observational study* (N=22; n=13)†</th>
<th>Retrospective case series (n=10)¹</th>
<th>Combined prospective trial and retrospective review (n=24)²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[Madan et al, 2016]</td>
<td>[Tumin et al, 2017]</td>
<td>[Filippone et al, 2016]</td>
<td>[Hogan et al, 2013]</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Hyperglycemia (n=2)</td>
<td>Swelling (n=1)</td>
<td>Hypertension (n=2)</td>
<td>Weight gain (n=4)</td>
</tr>
<tr>
<td></td>
<td>Weight gain (n=1)</td>
<td>Hypertension (n=2)</td>
<td>Edema (n=5)</td>
<td>Hypertension (n=2)</td>
</tr>
<tr>
<td></td>
<td>Swelling (n=1)</td>
<td>Hypertension (n=2)</td>
<td>Insomnia (n=2)</td>
<td>Weight gain (n=4)</td>
</tr>
<tr>
<td>Early termination</td>
<td>Edema (n=1)</td>
<td>Reasons not given (n=1)</td>
<td>Myalgia, weight gain, and worsening diabetes (n=1)</td>
<td>Myalgia, weight gain, and worsening diabetes (n=1)</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia (n=2)</td>
<td>Hyperglycemia (n=5)</td>
<td>Edema (n=1)</td>
<td>Edema and hypertension (n=1)</td>
</tr>
<tr>
<td></td>
<td>Edema (n=1)</td>
<td>Edema (n=1)</td>
<td>Fatigue (n=1)</td>
<td>New-onset diabetes (n=1)</td>
</tr>
</tbody>
</table>

*Safety results were pooled and presented for all 22 patients; investigators did not distinguish whether they were observed in the MN or FSGS populations.
†This trial includes longer-term follow-up data for 4 patients from previous trials (2 with FSGS, 2 with MN): 1 patient from the Bomback 2011 dataset and 3 patients from the Hogan 2013 trial.

- Across multiple FSGS datasets, adverse events were considered tolerable with nearly 90% of patients completing the full prescribed course of Acthar Gel.²
  - Early termination occurred in 5 of 62 patients and was due to increased swelling (n=1); new-onset diabetes (n=1); myalgia, weight gain, and worsening diabetes (n=1); edema and hypertension (n=1); and for reasons not given (n=3).²,³

**IMPORTANT SAFETY INFORMATION**

**Contraindications**
- Acthar should never be administered intravenously
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar
- Acthar is contraindicated where congenital infections are suspected in infants
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenal cortical insufficiency, adrenal cortical hyperfunction, or sensitivity to proteins of porcine origin

**Warnings and Precautions**
- The adverse effects of Acthar are related primarily to its corticosteroidic effects
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- Suppression of the hypothalamic-pituitary-adrenal (HPA) axis may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA suppression after stopping treatment
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- Patients with comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar in patients with diabetes and myasthenia gravis
- Prolonged use of Acthar may produce cataracts, glaucoma, and secondary ocular infections. Monitor for signs and symptoms
- Acthar is immunogenic and prolonged administration of Acthar may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH activity
- There is an enhanced effect in patients with hypothryroidism and in those with cirrhosis of the liver
- Long-term use may have negative effects on growth and physical development in children. Monitor pediatric patients
- Decrease in bone density may occur. Bone density should be monitored for patients on long-term therapy
- Pregnancy Class C. Acthar has been shown to have an embryocidal effect and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

**Adverse Reactions**
- Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain
- Specific adverse reactions reported in US clinical trials in infants and children under 2 years of age included: infection, hypertension, irritability, Cushingoid symptoms, constipation, diarrhea, vomiting, pyrexia, weight gain, increased appetite, decreased appetite, nasal congestion, acne, rash, and cardiac hypertrophy. Conversions were also reported, but these may actually be occurring because some US patients progress to other forms of seizures and US sometimes masks other seizures, which become visible once the clinical spasms from IS resolve

Other adverse events reported are included in the accompanying full Prescribing Information. Please see the accompanying full Prescribing Information.
Acthar Gel offers a treatment option for proteinuria reduction in patients with post-transplant FSGS

Potential mechanism of action
- Acthar Gel is believed to work by binding to receptors on podocytes on the kidney and hyperimmune immune cells during active disease and stimulates low levels of cortisol release.

Clinical experience and data in post-transplant FSGS
- Clinical data in 34 patients with post-transplant FSGS, the majority of whom were previously treated and had varying renin functional status.
- Greater than 50% reduction in proteinuria in patients with post-transplant FSGS, with 36% and 50% of patients achieving CR or PR using their respective definitions of CR and PR.
- See safety findings and study limitations on pages 5-7

Clinical evidence and data in native kidney FSGS
- Clinical data in over 60 FSGS patients with nephrotic-range proteinuria, the majority of whom were previously treated, and who had varying renin functional status.
- In the datasets presented, 29%-69% of patients taking Acthar Gel experienced reductions in proteinuria.
- Four out of five studies included stable or improved renin function as part of the definition of remission.
- See safety findings and study limitations on pages 8-10

Dosing
- The usual dose of Acthar Gel is 40-80 units given intramuscularly or subcutaneously every 24-72 hours.

Please see additional Important Safety Information throughout and on page 10.
Please see accompanying Full Prescribing Information.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions
- The adverse effects of Acthar are related primarily to its steroidogenic effects.
- Acthar may increase susceptibility to new infection or reactivation of latent infections.
- Suppression of the hypothalamic-pituitary-adrenal (HPA) axis may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress.

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References
7. Wright, D., Fitch, R. Acthar® Gel (repository corticotropin injection) enhancement remyelination after cuprizone-induced demyelination. Poster presented at: Consortium of Multiple Sclerosis Centers Annual Meeting; May 28-June 1, 2019; Seattle, WA.
10. Tumlin, J., Galphin, C., Santos, R., Rovin, B. Data on file: ARDUS/01-03/0218/0013. Mallinckrodt ARD LLC.
Acthar® Gel

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Acthar® Gel safely and effectively. See full prescribing information for Acthar Gel.

Acthar Gel (repository corticotropin injection) INJECTION, GEL for INTRAMUSCULAR or SUBCUTANEOUS use
Initial U.S. Approval: 1952

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**INDICATIONS AND USAGE**

- **Infantile Spasms:** Acthar Gel is indicated for the treatment of infantile spasms in infants and children under 2 years of age. (1.1)
- **McArdle's Disease:** Acthar Gel is indicated for the treatment of the myophosphorylase deficiency of McArdle's disease in adult patients. (1.2)

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**DOSAGE AND ADMINISTRATION**

- 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. (2.1)

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**CONTRAINDICATIONS**

- Acthar Gel should never be given intravenously.
- Acthar Gel is contraindicated in patients with 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.

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**ADVERSE REACTIONS**

- **Common adverse reactions for Acthar Gel are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.** (6)

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**PATIENT COUNSELING INFORMATION**

- Adrenal Insufficiency after Prolonged Therapy: Monitor for effects of hypothalamic-pituitary-axis suppression after stopping treatment. (5.2)

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**FULL PRESCRIBING INFORMATION**

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- 5 mL multi-dose vial containing 80 USP units per mL. (3)

4 CONTRAINDICATIONS

- Acthar Gel should never be given intravenously.
- Acthar Gel is contraindicated in patients with 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.

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FDA-approved Medication Guide

Revised: 3/2019
Acthar Gel (repository corticotropin injection) is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.

### 1.2 Multiple Sclerosis
Acthar Gel (repository corticotropin injection) is indicated for the treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that reflects the ultimate outcome or natural history of the disease.

### 1.3 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.

### 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
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.

### 2.1 Specific Recommended Dosage Regimen for Infantile Spasms in Infants and Children Under 2 Years of Age
In the treatment of infantile spasms, Acthar Gel must be administered intramuscularly. The recommended regimen is a daily dose of 150 U/m² (divided into twice daily intramuscular injections of 75 U/m²) administered over a 2-week period. Dosing with Acthar Gel should then be gradually tapered over a 2-week period to avoid adrenal insufficiency. 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; 5 U/m² in the morning for 3 days; and 10 U/m² every other morning for 6-days.

Acthar Gel is typically dosed based on body surface area (BSA). For calculation of body surface area, use the following formula:

$$\text{BSA (m}^2) = \frac{\text{weight (kg)} \times \text{height (cm)}}{3600}$$

### 2.2 Recommended Dosage Regimen for the Treatment of Acute Exacerbations in Adults with Multiple Sclerosis
The recommended dose is daily intramuscular or subcutaneous doses of 80-120 units for 2-3 weeks for acute exacerbations.

Dosage should be individualized according to the medical condition of each patient. Frequency and dose of the drug should be determined by considering the severity of the disease and the initial response of the patient. Although drug dependence does not occur, sudden withdrawal of Acthar Gel after prolonged use may lead to adrenal insufficiency or recurrent symptoms which make it difficult to stop the treatment. It may be necessary to taper the dose and increase the injection interval to gradually discontinue the medication.

### 2.3 Recommended Dosage Regimen for 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. Frequency and dose of the drug should be determined by considering severity of the disease and the initial response of the patient.

The usual dose of Acthar Gel is 40-80 units given intramuscularly or subcutaneously every 24-72 hours.

Although drug dependence does not occur, sudden withdrawal of Acthar Gel after prolonged use may lead to adrenal insufficiency or recurrent symptoms which make it difficult to stop the treatment. It may be necessary to taper the dose and increase the injection interval to gradually discontinue the medication.

### 2.4 Preparation
Acthar Gel should be warmed to room temperature before using. Caution should be taken not to over-pressurize the vial prior to withdrawing the product.

### 3 DOSAGE FORMS AND STRENGTHS
5 mL multi-dose vial containing 80 USP Units per mL.

### 4 CONTRAINDICATIONS
Acthar Gel is contraindicated for intravenous administration.

Acthar Gel is contraindicated where congenital infections are suspected in infants. Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel.

Acthar Gel is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origin.

### 5 WARNINGS AND PRECAUTIONS
The adverse effects of Acthar Gel are related primarily to its steroidogenic effects. Not all of the adverse events described below have been seen after treatment with Acthar Gel, but might be expected to occur [see Adverse Reactions (6.3)].

#### 5.1 Infections
Adrenal steroid may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan or hemlichnemic infections. Patients with latent tuberculosis or tuberculosis reactivity should be observed closely, and if therapy is prolonged, chemoprophylaxis should be instituted.

#### 5.2 Cushing’s Syndrome and Adrenal Insufficiency Upon Withdrawal
Treatment with Acthar Gel can cause hypothalamic-pituitary-axis (HPA) suppression and Cushing’s syndrome. These conditions should be monitored especially with chronic use. Suppression of the HPA may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Patients should be monitored for signs of insufficiency such as weakness, hyperpigmentation, weight loss, hypotension and abdominal pain.

The symptoms of adrenal insufficiency in infants treated for infantile spasms can be difficult to identify. The symptoms are non-specific and may include anorexia, fatigue, lethargy, weakness, excessive weight loss, hypotension and abdominal pain. It is critical that parents and caregivers be made aware of the possibility of adrenal insufficiency when discontinuing Acthar Gel and should be instructed to observe for, and be able to recognize, these symptoms [see Patient Counseling Information (17)].

The recovery of the adrenal gland may take from days to months so patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids during the period of stress.

The adrenal insufficiency may be minimized in adults and infants by tapering of the dose when discontinuing treatment.

Symptoms or features of Cushing’s syndrome may occur during therapy but generally resolve after therapy is stopped. Patients should be monitored for these signs and symptoms such as deposition of adipose tissue in characteristic sites (e.g., moon face, truncal obesity), cutaneous striae, easy bruising, decreased bone mineralization, weight gain, muscle weakness, hyperglycemia, and hypertension.

#### 5.3 Elevated Blood Pressure, Salt and Water Retention and Hypokalemia
Acthar Gel can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. Dietary salt restriction and potassium supplementation may be necessary. Caution should be used in the treatment of patients with hypertension, congestive heart failure, or renal insufficiency.

#### 5.4 Vaccination
Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel. Killed or inactivated vaccines may be administered; however, the response to such vaccines can not be predicted. Other immunization procedures should be undertaken with caution in patients who are receiving Acthar Gel, especially when high doses are administered, because of the possible hazards of neurological complications and lack of antibody response.

#### 5.5 Masking Symptoms of Other Diseases
Acthar Gel often acts by masking symptoms of other diseases/disorders without altering the course of the other disease/disorder. Patients should be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight and fecal blood loss.

#### 5.6 Gastrointestinal Perforation and Bleeding
Acthar Gel can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Signs of gastrointestinal perforation, such as peritoneal irritation, may be masked by the therapy. Use caution where there is the possibility of impeding perforation, abscess or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer.

#### 5.7 Behavioral and Mood Disturbances
Use of Acthar Gel may be associated with central nervous system effects ranging from euphoria, insomnia, irritability (especially in infants), mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated.

#### 5.8 Comorbid Diseases
Patients with a comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar Gel in patients with diabetes and myasthenia gravis.

#### 5.9 Ophthamologic Effects
Prolonged use of Acthar Gel may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungus and viruses.

#### 5.10 Immunogenicity Potential
Acthar Gel is immunogenic. Limited available data suggest that a patient may develop antibodies to Acthar Gel after chronic administration and loss of endogenous ACTH and Acthar Gel activity. Prolonged administration of Acthar Gel may increase the risk of hypersensitivity reactions. Sensitivity to porcine protein should be considered before starting therapy and during the course of treatment should symptoms arise.

#### 5.11 Use in Patients with Hypothyroidism or Liver Cirrhosis
There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver.

5 WARNINGS AND PRECAUTIONS

The adverse effects of Acthar Gel are related primarily to its steroidogenic effects. Not all of the adverse events described below have been seen after treatment with Acthar Gel, but might be expected to occur [see Adverse Reactions (6.3)].
5.12 Negative Effects on Growth and Physical Development

Long-term use of Acthar Gel may have negative effects on growth and physical development in children. Changes in appetite are seen with Acthar Gel therapy, with the effects becoming more frequent as the dose or treatment period increases. These effects are reversible once Acthar Gel therapy is stopped. Growth and physical development of pediatric patients on prolonged therapy should be carefully monitored.

5.13 Decrease in Bone Density

Decrease in bone formation and an increase in bone resorption both through an effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function may occur. These, together with a decrease in the protein matrix of the bone (secondary to an increase in protein catabolism) and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and to the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating therapy, and bone density should be monitored in patients on long term therapy.

5.14 Use in Pregnancy

Acthar Gel has been shown to have an embryocidal effect. Apprise women of potential harm to the fetus [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

Please refer to Adverse Reactions in Infants and Children Under 2 Years of Age (Section 6.1.1) for consideration when treating patients with Infantile Spasms. The adverse reactions presented in Section 6.2 are primarily provided for consideration in use in adults and in children over 2 years of age, but these adverse reactions should also be considered when treating infants and children under 2 years of age.

Acthar Gel causes the release of endogenous cortisol from the adrenal gland. Therefore, all the adverse effects known to occur with elevated cortisol may occur with Acthar Gel administration as well. Common adverse reactions include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

6.1.1 Adverse Reactions in Infants and Children Under 2 Years of Age

While the types of adverse reactions seen in infants and children under age 2 treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Below is a summary of adverse reactions specifically tabulated from source data derived from retrospective chart reviews and clinical trials in children under 2 years of age treated for infantile spasms. The number of patients in controlled trials at the recommended dose was too few to provide meaningful incidence rates or to permit a meaningful comparison to the control groups.

TABLE: Incidence (%) of Treatment Emergent Adverse Events Occurring in ≥ 2% of Acthar Gel (repository corticotropin injection) Infants and Children under 2 years of Age

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Recommended 75 U/m² bid n=122, (%)</th>
<th>150 U/m² qd n=37 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Hypertrophy</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Convulsion†</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Acne</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

* Specific infections that occurred at ≥ 2% were candidiasis, otitis media, pneumonia and upper respiratory tract infections. † In the treatment of Infantile Spasms, other types of seizures/convulsions may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally, the spasms sometimes mask other seizures and once the spasms resolve after treatment, the other seizures may become visible.

These adverse reactions may also be seen in adults and children over 2 years of age when treated for other purposes and with different doses and regimens.

6.2 Postmarketing Experience

The following adverse reactions associated with the use of Acthar Gel have been identified from postmarketing experience with Acthar Gel. Only adverse events that are not listed above as adverse events reported from retrospective chart reviews and non-sponsor conducted clinical trials and those not discussed elsewhere in labeling, are listed in this section. Because the adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to use with Acthar Gel. Events are categorized by system organ class. Unless otherwise noted these adverse events have been reported in infants, children and adults.

6.2.1 Allergic Reactions

Allergic responses have presented as dizziness, nausea and shock (adults only).

6.2.2 Cardiovascular

Necrotizing angitis (adults only) and congestive heart failure.

6.2.3 Dermatologic

Skin thinning (adults only), facial erythema and increased sweating (adults only).

6.2.4 Endocrine

Decreased carbohydrate tolerance (infants only) and hirsutism.

6.2.5 Gastrointestinal

Pancreatitis (adults only), abdominal distention and ulcerative esophagitis.

6.2.6 General Disorders and Administration Site Conditions

Injection site reactions.

6.2.7 Metabolic

Hypokalemia (infants only).

6.2.8 Musculoskeletal

Muscle weakness and vertebral compression fractures (infants only).

6.2.9 Neurological

Headache (adults only), vertigo (adults only), subdural hematoma, intracranial hemorrhage (adults only), and reversible brain shrinkage (usually secondary to hypertension) (infants only).

6.3 Possible Additional Steroidogenic Effects

Based on steroidogenic effects of Acthar Gel certain adverse events may be expected due to the pharmacological effects of corticosteroids. The adverse events that may occur but have not been reported for Acthar Gel are:

6.3.1 Dermatologic

Impaired wound healing, abscess, petechiae and ecchymoses, and suppression of skin test reactions.

6.3.2 Endocrine

Menstrual irregularities.

6.3.3 Metabolic

Negative nitrogen balance due to protein catabolism.

6.3.4 Musculoskeletal

Loss of muscle mass and aseptic necrosis of femoral and humeral heads.

6.3.5 Neurological

Increased intracranial pressure with papilledema, (pseudo-tumor cerebri) usually after treatment, and subdural effusion.

6.3.6 Ophthalmic

Exophthalmos.

7 DRUG INTERACTIONS

Formal drug-drug interaction studies have not been performed. Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Class C: Acthar Gel has been shown to have an embryocidal effect. There are no adequate and well-controlled studies in pregnant women. Acthar Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Acthar Gel, when treating a nursing mother, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk and benefit to the mother.
8.4 Pediatric Use
Acthar Gel is indicated as monotherapy for the treatment of infantile spasms in infants and children less than 2 years of age. Both serious and other adverse reactions in this population are discussed in Warnings and Adverse Reactions in Infants and Children Under 2 Years of Age [see Sections 5 and 6.1.1].

The efficacy of Acthar Gel for the treatment of infantile spasms in infants and children less than 2 years of age was evaluated in a randomized, single blinded (video EEG interpreted blinded) clinical trial and an additional active control supportive trial [see Clinical Studies (14)]. A responding patient was defined as having both complete cessation of spasms and elimination of hypsarrhythmia.

Safety in the pediatric population for infantile spasms was evaluated by retrospective chart reviews and data from non-sponsor conducted clinical trials [see Adverse Reactions (6.1.1)]. While the types of adverse reactions seen in infants and children under 2 years of age treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Effects on growth are of particular concern [see Warnings and Precautions (5.12)]. Serious adverse reactions observed in adults may also occur in children [see Warnings and Precautions (5)].

10 OVERDOSAGE
While chronic exposure to Acthar Gel at high doses can be associated with a variety of potential serious adverse effects, it is not expected that a single high dose, or even several large doses, would have the potential for serious adverse effects compared to a standard dose. There have been no reports of death or acute overdose symptoms from Acthar Gel in clinical studies or in the published literature.

The intramuscular route of administration makes it unlikely that an inadvertent acute overdose will occur. The typical daily dose of Acthar Gel to treat an infant that has a BSA of 0.4 m² would be 60 U/day. Using the 1-cc syringe supplied with Acthar Gel, the maximum amount that can be injected is 80 Unijection, which is a well-tolerated single dose.

11 DESCRIPTION
Acthar Gel is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides. The Acthar Gel manufacturing process converts the initial porcine pituitary extract with ACTH content into a mixture having modified porcine ACTH and other related peptide analogs solubilized in gelatin. A major component in the formulated complex mixture is N-25 deamidated porcine ACTH (1-39).

Acthar Gel is supplied as a sterile preparation in 16% gelatin to provide a prolonged release after intramuscular or subcutaneous injection. Acthar Gel also contains 0.5% phenol, not more than 0.1 mg cysteine (added), sodium hydroxide and/or acetic acid to adjust pH and water for injection.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The mechanism of action of Acthar Gel in the treatment of infantile spasms is unknown. Acthar Gel and endogenous ACTH stimulate the adrenal cortex to secrete cortisol, corticosterone, aldosterone and a number of weak androgenic substances. Prolonged administration of large doses of Acthar Gel increases hyperplasia and hypertrophy of the adrenal cortex and continuous high output of cortisol, corticosterone and weak androgens. The release of endogenous ACTH is under the influence of the nervous system via the regulatory hormone released from the hypothalamus and by a negative corticosteroid feedback mechanism. Elevated plasma cortisol suppresses ACTH release.

Acthar Gel is also reported to bind to melanocortin receptors. The trophic effects of endogenous ACTH and Acthar Gel on the adrenal cortex are not well understood beyond the fact that they appear to be mediated by cyclic AMP. ACTH rapidly disappears from the circulation following its intravenous administration; in people, the plasma half-life is about 15 minutes. The pharmacokinetics of Acthar Gel have not been adequately characterized.

The maximal effects of a trophic hormone on a target organ are achieved when optimal amounts of hormone are acting continuously. Thus, a fixed dose of Acthar Gel will demonstrate a linear increase in adrenocortical secretion with increasing duration for the infusion.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate and well-controlled studies have not been done in animals. Human use has not been associated with an increase in malignant disease [see Warnings and Precautions (5.14) and Use in Specific Populations (8.1)].

14 CLINICAL STUDIES
The effectiveness of Acthar Gel as a treatment for infantile spasms was demonstrated in a single blinded (video EEG interpreter blinded) clinical trial in which patients were randomized to receive either a 2 week course of treatment with Acthar Gel (75 U/m² intramuscular twice daily) or prednisone (1 mg/kg by mouth twice daily). The primary outcome was a comparison of the number of patients in each group who were treatment responders, defined as a patient having complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG performed 2 weeks following treatment initiation, rated by an investigator blinded to treatment. Thirteen of 15 patients (86.7%) responded to Acthar Gel as compared to 4 of 14 patients (28.6%) given prednisone (p<0.002). The 2-week treatment was followed by a 2-week period of taper. Nonresponders to the prednisone treatment were eligible to receive Acthar Gel treatment. Seven of 8 patients (87.5%) responded to Acthar Gel after not responding to prednisone. Similarly, the 2 nonresponder patients from the Acthar Gel treatment were eligible to receive treatment with prednisone. One of the 2 patients (50%) responded to the prednisone treatment after not responding to Acthar Gel.

A supportive single-blind, randomized clinical trial comparing high-dose, long-duration treatment (150 U/m² once daily for 3 weeks, n=30) of Acthar Gel with low-dose, short-duration treatment (20 U once daily for 2 weeks, n=29) for the treatment of infantile spasms was also evaluated in infants and children less than 2 years of age. Nonresponders (defined as in the previously described study) in the low-dose group received a dose escalation at 2 weeks to 30 U once daily. Nominal statistical superiority of the high dose treatment, as compared to the low dose treatment, was observed for cessation of spasms but not for the resolution of hypsarrhythmia.

16 HOW SUPPLIED / STORAGE AND HANDLING
Acthar Gel (repository corticotropin injection) is supplied as 5 mL multi-dose vial (63004-8710-1) containing 80 USP Units per mL. Acthar Gel (repository corticotropin injection) should be warmed to room temperature before using. Do not over pressurize the vial prior to withdrawing the product.

Store Acthar Gel (repository corticotropin injection) under refrigeration between 2° to 8°C (36° to 46°F). Product is stable for the period indicated on the label when stored under the conditions described.

17 PATIENT COUNSELING INFORMATION
Caregivers of patients with infantile spasms should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to administering Acthar Gel. Patients should be instructed to take Acthar Gel only as prescribed. They should not stop treatment suddenly unless instructed by their physician to do so.

Patients, their caregivers and families should be advised as to the importance of the need for careful monitoring while on and during titration from Acthar Gel treatment and the importance of not missing scheduled doctor’s appointments.

Patients, their caregivers and families should be advised that if the patient develops an infection they should contact their physician. They should be educated that a fever may not necessarily be present during infection. The patient should also try to limit contact with other people with infections to minimize the risk of infection while taking Acthar Gel [see Warnings and Precautions (5.1) and Adverse Reactions (6.1.1)].

Patients, their caregivers and families should be advised that if the patient experiences an increase in blood pressure they should contact their physician [see Warnings and Precautions (5.1) and Adverse Reactions (6.1.1)].

Patients, their caregivers and families should be advised that the patient may be monitored for signs of adrenal insufficiency such as weakness, fatigue, lethargy, anorexia, weight loss, hypotension, abdominal pain or hyperpigmentation (adults only) after treatment has stopped. Since the recovery of the adrenal gland varies from days to months, patients may need to be protected from the stress of trauma or surgery by the use of corticosteroids during the period of stress [see Warnings and Precautions (5.2)].

Patients should be advised not to be vaccinated with live or live attenuated vaccines during treatment with Acthar Gel. Additionally, other immunization procedures in patients or in family members who will be in contact with the patient should be undertaken with caution while the patient is taking Acthar Gel [see Warnings and Precautions (5.4)].

Patients, their caregivers and families should be advised that prolonged use of Acthar Gel in children may result in Cushing’s syndrome and associated adverse reactions, may inhibit skeletal growth, and may cause osteoporosis and decreased bone density. If prolonged use is necessary, Acthar Gel should be given intermittently along with careful observation [see Warnings and Precautions (5.2), (5.12), (5.13) and Adverse Reactions (6.1.1)].

Patients, their caregivers and families should be informed that Acthar Gel may mask symptoms of other diseases/disorders without altering the course of the other disease/disorder. The patient will need to consult the patient’s physician during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight, and fecal blood loss [see Warnings and Precautions (5.5)].

In the treatment of Infantile Spasms, other types of seizures may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment with Acthar Gel, the other seizures may become visible. Parents and caregivers should inform their physician of any new onset of seizures so that appropriate management can then be instituted [see Adverse Reactions (6.1.1)].

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