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.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

Post-transplant FSGS is a serious concern

Prevalence and progression of FSGS

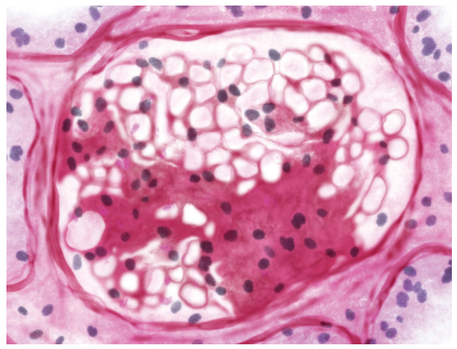
Prevalence in patients with FSGS[1] (native kidney)	Relapse rate[2] (native kidney)	Rate of progression to ESRD[3] (native kidney)	Recurrence in post-renal transplantation[4]
43%	40%	Up to 60%	Overall 20%-50% May exceed 80% with history of graft loss

- 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]

High-risk factors for recurrence[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

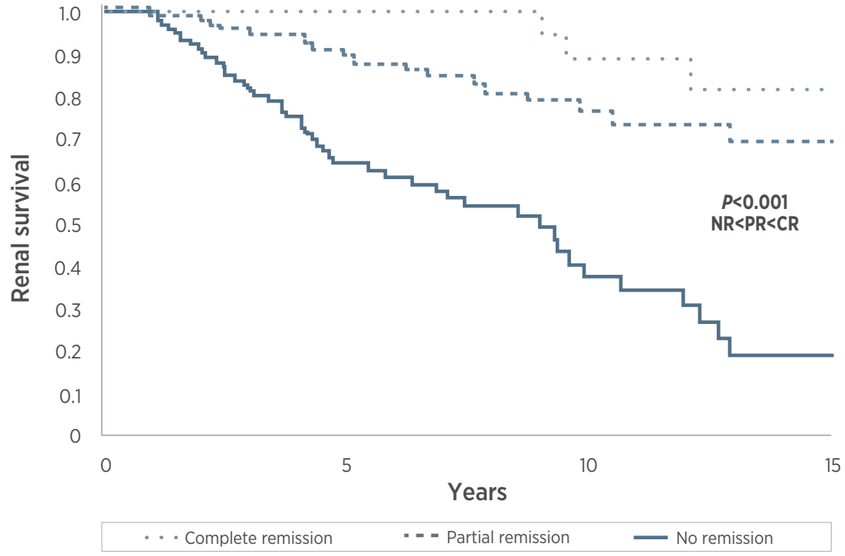


ESRD=end-stage renal disease; FSGS=focal segmental glomerulosclerosis.

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]



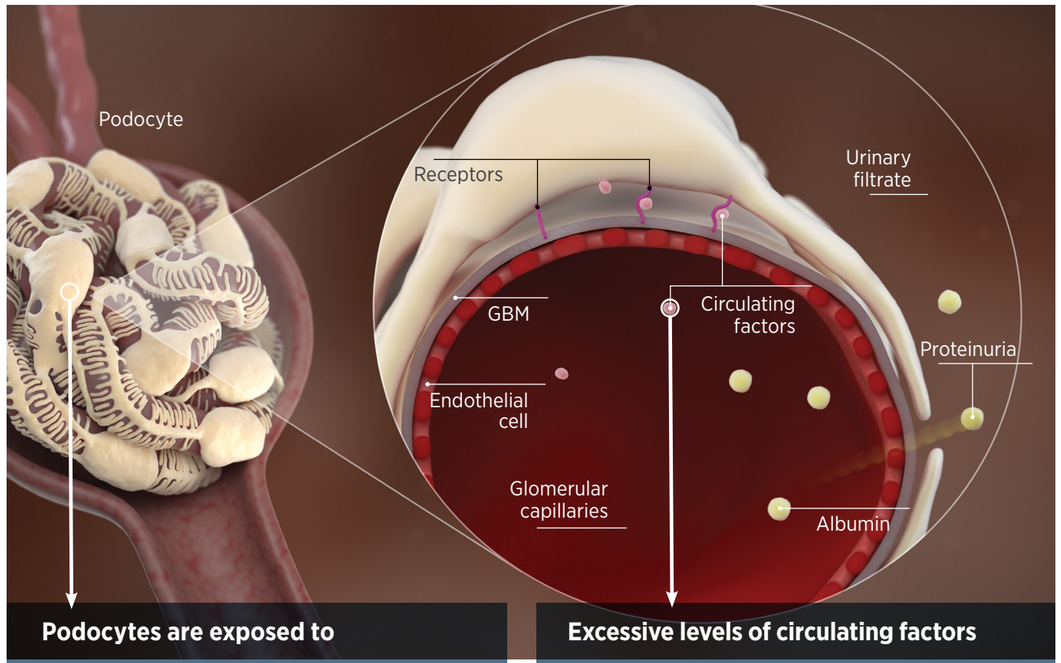
Adapted from Troyanov et al.[10]

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.

Circulating factors targeting podocytes may be involved in FSGS recurrence after kidney transplantation



Podocytes are exposed to

circulating factors that penetrate the endothelium and glomerular basement membrane (GBM) layers[11]

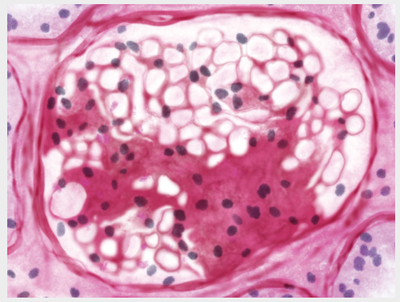
Excessive levels of circulating factors

have been associated with podocyte injury and dysfunction of the glomerular filtration barrier[11,12]

Management of recurrent FSGS remains a significant problem among post-transplant patients

Post-transplant FSGS diagnosis

- There is a lack of a standardized protocol for the management of proteinuria following transplant[4,13]
- Evidence-based treatment options are limited[5]
- Current options are supported by data from small studies and case reports[5]



First-line treatment

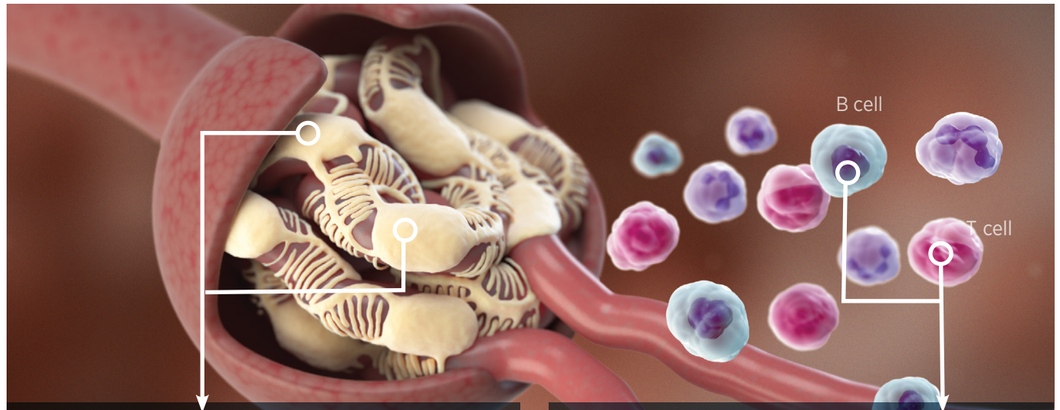
Conventional approaches to post-transplant FSGS treatment involve different therapeutic mechanisms[5]

- 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* directly on podocytes and immune cells



Direct Effects on Podocytes in the Kidney

Binds directly to receptors on podocytes

- Stabilizing synaptopodin, a podocyte-specific protein that helps maintain the structure of the podocyte actin cytoskeleton[14-17]
- Reducing podocyte foot process effacement and podocyte apoptosis[14,18]
- Improving histologic signs of renal injury[18]
- Reducing glomerular permeability[18]

Modulation of the Immune Response

Binds to hyperactive immune cells during active disease

- Downregulating proinflammatory response pathways to diminish expression of inflammatory mediators implicated in the immune response[18,19]
- Regulating autoantibody production by modulating hyperactive T and B lymphocytes[19]
- Restoring the balance of immune cell populations[18]

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]

MP=methylprednisolone; PD=pharmacodynamics; SC=subcutaneous; TEAE=treatment-emergent adverse event.

*Melanocortin receptor pathway.

†**MNK14314065 study design, safety findings, and study limitations:** An open-label, single-center, randomized, multiple-dose parallel group study to compare the PD and safety of intermittent doses of Acthar Gel to daily oral MP in healthy subjects. Patients between 18 and 50 years old were randomized to receive Acthar Gel 40 or 80 units SC 2 times per week for 15 days (n=12/group) or 16 mg of oral MP given once daily for 15 days (n=12), followed by a tapering regimen of 8 mg daily for 2 days, and then 4 mg daily for 2 days. The most frequently reported TEAEs that occurred in 2 or more subjects were (in decreasing order of frequency): injection-site hemorrhage, headache, injection-site erythema, injection-site pruritus, insomnia, acne, infrequent bowel movements, and injection-site pain. All TEAEs experienced during this study were considered mild in severity. As this was a healthy subject, open-label study with no placebo control, the clinical relevance of differences in tolerability is unknown and remains to be investigated for patient populations.[20]

SELECT IMPORTANT SAFETY INFORMATION

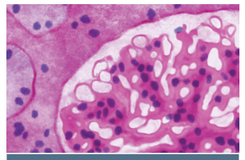
Warnings and Precautions

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

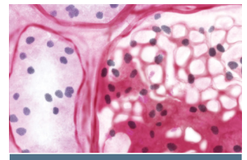
Please see additional Important Safety Information throughout and on page 10.
Please see accompanying full Prescribing Information.

Published Clinical Data Describe Acthar Gel in Over 200 Patients, the Majority of Whom Were Previously Treated With First-line Therapy[4,25-33,35]

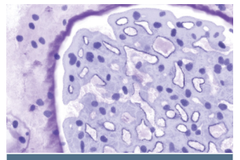
Acthar Gel Has Clinical Experience Across a Spectrum of NS Etiologies



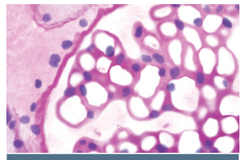
IgAN (n=30)



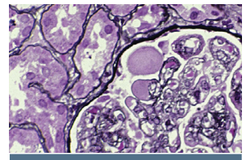
FSGS (n=96)
Post-transplant (n=34)
Native kidney (n=62)



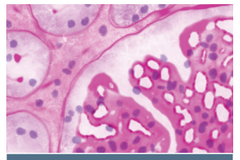
iMN (n=56)



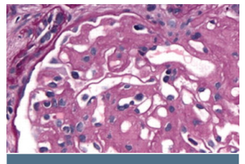
MCD (n=8)



MPGN (n=5)



LN (n=3)



FGN (n=1)

Unbiopsied NS (n=4)

Monoclonal DPGN (n=1)

Acthar Gel is indicated to induce a diuresis or a **remission of proteinuria in NS** without uremia of the idiopathic type or that due to lupus erythematosus[34]

Clinical parameters that helped characterize patients with FSGS included severity of proteinuria, renal impairment, and previous IST[4,26-32,35]

Patients with nephrotic-range proteinuria

Native kidney FSGS[26-28,30,31,35-37] (n=62)

Renal impairment
- **Serum creatinine:** study average from 1.0 mg/dL to 2.3 mg/dL
- **eGFR:** study average from 33 mL/min/1.73 m² to >90 mL/min/1.73 m²

Received ≥1 prior treatment‡
- 88% had ≥1 previous IST

Post-transplant FSGS[4,32] (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 m² to 36.5 mL/min/1.73 m²

Received ≥1 prior treatment‡
- 74% received TPE +/- rituximab

‡Previous IST may have included ≥1 of the following: steroids, CNI, MMF, CTX, cyclosporine, tacrolimus, rapamycin, abatacept, chlorambucil, methotrexate, azathioprine, pentoxifylline, and/or rituximab. Other than steroids, listed therapies are not approved for the reduction of proteinuria in NS.

CTX=cyclophosphamide; DPGN=diffuse proliferative glomerulonephritis; eGFR=estimated glomerular filtration rate; FGN=fibrillary glomerulonephritis; IgAN=IgA nephropathy; iMN=idiopathic membranous nephropathy; IST=immunosuppressive therapy; LN=lupus nephritis; MCD=minimal change disease; MMF=mycophenolate mofetil; MPGN=membranoproliferative glomerulonephritis.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

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[32]

Overview[32]

- 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

Pre-Acthar Gel treatment patient data[32]	
Mean baseline proteinuria (N=14)	7.3 g/g (range: 2.26 to 38.0 g/g)
Mean baseline eGFR (n=13)*	36.5 mL/min/1.73 m^2 (range: 18 to 59 mL/min/1.73 m^2)
Mean baseline SCr (N=14)	2.4 mg/dL (range: 1.12 to 5.24 mg/dL)
Mean time from kidney transplant to Acthar Gel (N=14)	16 months (range: 0 to 53.4 months)
Mean time from FSGS diagnosis post-transplant to Acthar Gel (N=14)	5 months (range: 0 to 34.9 months)
Prior kidney transplant (N=14)	3 patients

*1 patient with eGFR <10 mL/min/1.73 m^2 at baseline was excluded from the analysis.

Treatment history[32]

- While 71% (10/14) of patients received plasmapheresis, only 14% (2/14) of patients received rituximab in addition to prednisone and plasmapheresis as part of their treatment for post-transplant FSGS

Post-transplant management[32]			Post-transplant FSGS management[32]	
Induction therapy after transplant	**Anti-rejection maintenance therapy after transplant**		**Treatment for post-transplant FSGS prior to Acthar Gel**	
• 57% (8/14) of patients received alemtuzumab • 43% (6/14) received ATG	• All 14 patients were treated with MMF • 64% (9/14) of patients were maintained with prednisone as part of their treatment regimen • 36% (5/14) of patients were placed on MMF and tacrolimus	• 14% (2/14) of patients were treated with MMF and prednisone • 50% (7/14) of patients received triple immunosuppression, which included MMF + prednisone + abatacept, belatacept, cyclosporine, OR tacrolimus	• 71% (10/14) of patients received PP • 21% (3/14) of patients did not receive any treatment • 21% (3/14) of patients received belatacept and PP	• 14% (2/14) of patients received PP, rituximab, and prednisone • 14% (2/14) of patients received abatacept and PP • 1 patient (7%) received treatment with prednisone only

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont.)

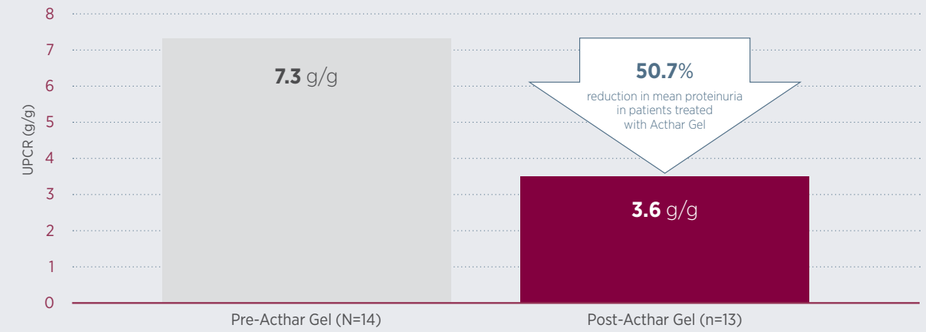
- Suppression of the hypothalamic-pituitary-adrenal (HPA) axis may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal 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

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

Clinical Data in Post-transplant FSGS [Grafals et al, 2019]

Proteinuria was reduced to remission levels in post-transplant FSGS patients following Acthar Gel treatment

Change in proteinuria following Acthar Gel treatment†[32]



†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.

Remission criterion: UPCR <0.50 g/g‡ — Grafals et al, 2019 publication outcome[32]	
Remission	**36%** (5/14)
Complete	21% (3/14)
Partial	15% (2/14)

Remission criterion: UPCR ≤1.0 g/g§ — Post hoc analysis outcome[32]	
Remission	**50%** (7/14)
Complete	29% (4/14)
Partial	21% (3/14)

UPCR=urine protein/creatinine ratio.

‡**Treatment outcome definitions from Grafals et al, 2019 publication.** Complete remission: final UPCR <0.50 g/g and serum creatinine ≤25% increase from baseline; and partial remission: ≥50% reduction in proteinuria with final UPCR between 0.50 and 3.50 g/g and serum creatinine ≤25% increase from baseline.

§**Treatment outcome definitions from the post hoc analysis.** The outcome measure as described in the Alhamad et al, 2019 publication. Complete remission: proteinuria ≤1 g/g with stable kidney function (creatinine within 30% from baseline); and partial remission: proteinuria 1.0 to 3.5 g/g with stable kidney function (creatinine within 30% from baseline).

Study dosing

The majority of patients (10/14) in this study received Acthar Gel 80 units subcutaneously, twice weekly for at least 6 months[32]

- Patients received a median of 6 months (range: 1-24 months) of Acthar Gel treatment during the study period[32]
  - The usual dose of Acthar Gel is 40-80 units given intramuscularly or subcutaneously every 24-72 hours[34]
- The dosage and frequency of Acthar Gel should be individualized according to the medical condition, severity of the disease, and initial response of the patient[34]

ATG=anti-thymocyte globulin; MMF=mycophenolate mofetil; PP=plasmapheresis.

Study limitations

This was a retrospective study with no control group, a small number of patients, and a lack of standardized study protocols for Acthar Gel and concurrent therapies. Results may not be solely attributable to Acthar Gel.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

Other observations reported for patients with post-transplant FSGS

Changes in renal function following Acthar Gel therapy in post-transplant FSGS patients*[32]

	Pre-Acthar Gel	Post-Acthar Gel
Mean SCr	2.4 mg/dL (N=14)	2.2 mg/dL (n=11)†
Mean eGFR	36.5 mL/min/1.73 m^2 (n=13)‡	45.2 mL/min/1.73 m^2 (n=11)§

*Calculations based on patients who had reported pre- and post-Acthar Gel values (adapted from Table 3: Acthar Gel Treatment Outcome).
†3 patients with ESRD were excluded from the analysis.
‡1 patient with eGFR <10 mL/min/1.73 m^2 at baseline was excluded from the analysis.
§3 patients with eGFR <10 mL/min/1.73 m^2 were excluded from the analysis.

Graft status‖[32]

Response type	N	No reported graft failure	Reported graft failure
Complete remission	3	3	0
Partial remission	2	2	0
No response	9	3	6
Total	14	8	6

‖Time from end of Acthar Gel treatment until graft failure ranged from 0 to 38 months. For functioning grafts, the authors did not collect the time interval from completion of Acthar Gel until the final assessment of graft status was made.

Safety findings in post-transplant patients with FSGS[32]

- 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

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

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[4]

Overview[4]

- 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[4]

Mean baseline proteinuria	8.6 ± 7.6 g/g
Mean baseline eGFR	30.7 ± 19.3 mL/min/1.73 m^2
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)[4]

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

Pre-transplant

Preventive protocol before transplant
- 20% (4/20) of patients received TPE before transplantation

Post-transplant

Preventive protocol after transplant
- 40% (8/20) of patients received rituximab within 24 hours of transplant

Anti-rejection treatment protocol after transplant
- All 20 patients were placed on triple immunosuppression
- 85% (17/20) were maintained throughout the observation period on MMF, prednisone, and tacrolimus
- 15% (3/20) were switched over to MMF, prednisone, and cyclosporine
- One (5%) then had CNI stopped because of calcineurin nephrotoxicity and was switched out to belatacept

Post-kidney transplant FSGS management

First-line treatment for post-transplant FSGS
TPE + rituximab + ACEi or ARB
- 75% (15/20) of patients received TPE
- 50% (10/20) of patients received rituximab and TPE

Study dosing[4]

The majority of patients (11/20) in this study received Acthar Gel 80 units subcutaneously, twice weekly for at least 6 months[4]

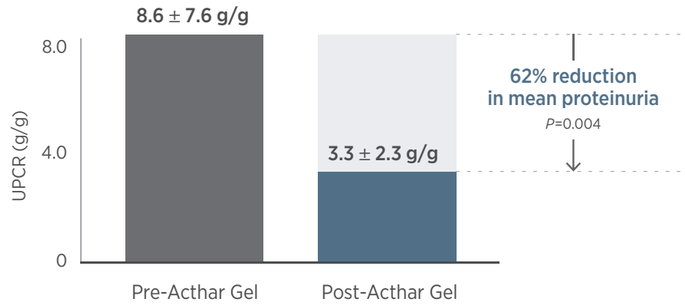
- The usual dose of Acthar Gel is 40-80 units given intramuscularly or subcutaneously every 24-72 hours¶[3,4]
- In Acthar Gel clinical datasets, the most common Acthar Gel dosing regimen was 80 units subcutaneously twice weekly for 6 months[26-31,35]

¶Dosage and frequency should be individualized according to the medical condition, severity of disease, and initial response of the patient.[37]
ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; IQR=interquartile range.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

Post-transplant patients taking Acthar Gel experienced a reduction in proteinuria to remission levels

Significant reduction in proteinuria (N=20)[4]



Post-transplant FSGS patients who were previously treated achieved remission[4]

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

Stable renal function was observed following Acthar Gel therapy*†[4]

	Baseline	Post-Acthar Gel	*P* value
Mean serum creatinine	3.3 ± 2.7 mg/dL	2.8 ± 1.67 mg/dL	*P*=0.42
Mean eGFR	30.7 ± 19.3 mL/min/1.73 m^2	34.4 ± 20 mL/min/1.73 m^2	*P*=0.56
Mean serum albumin	3.6 g/g	3.7 g/g	—

*Complete remission: proteinuria ≤1 g/g with stable kidney function (creatinine within 30% from baseline).
†Partial remission: proteinuria 1.0 to 3.5 g/g with stable kidney function (creatinine within 30% from baseline).

Safety findings[4]

- 8 patients had allograft failure during the follow-up period. 5 graft failures were attributed to recurrent or de novo FSGS despite use of Acthar Gel, 1 was complicated by cytomegalovirus disease, and 1 by JC nephropathy
- 1 patient died due to an aortic dissection while on therapy. 2 patients died during the post-therapy follow-up period

Study limitations

This was a retrospective study with no control group. Not all patients were treated similarly; this included some subjects who received initial prophylactic TPE or rituximab as a preventative measure at their treatment center. A variety of factors may have influenced the improvement in proteinuria, including TPE given with Acthar Gel.

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

Clinical Data in Post-transplant FSGS [Alhamad et al, 2019]

Other observations reported for patients with post-transplant FSGS

Graft status (2012-2016 observation period)[4]

Response type	N	No reported graft failure	Reported graft failure
Complete remission	4	4	0
Partial remission	6	4	2‡
No response	10	4	6§
Total	20	12	8

Therapeutic plasma exchange (TPE)[4]

	TPE utilization	
TPE utilization at completion of observation period	6 of 10 reported discontinued TPE	4 of 10 reported less frequent use of TPE

‡Graft failures reported 27 and 36 months after completion of Acthar Gel treatment.[4]
§Graft failure: 5 were attributed to recurrent or de novo FSGS despite the use of Acthar Gel, 1 was complicated also by cytomegalovirus disease, and 1 by JC nephropathy.[4]

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, Cushingoid symptoms, constipation, diarrhea, 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.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

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[26]

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 ≤125% of baseline or eGFR ≥75% of baseline). This compound outcome measure aligns with the KDIGO guidelines recommendations for assessing treatment response to NS therapy.

Patient characteristics[26,37]

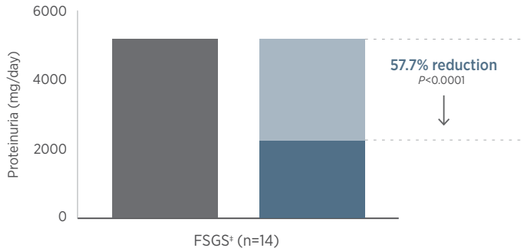
Mean baseline proteinuria‡	5238 mg/day (range: 2500-9306 mg/day)
Prior treatment history§	80% of patients (12/15) received ≥1 prior IST

Mean baseline serum creatinine‡	2.27 mg/dL (range: 0.9-4.8 mg/dL)

‡Calculation based on patients who had reported pre- and post-Acthar Gel values. Does not include 1 patient who terminated early due to AEs.

§IST included: steroids, cyclosporine, MMF, CTX, tacrolimus, rituximab, and/or methotrexate used either alone or in combination.
Other than steroids, listed therapies are not approved for the reduction of proteinuria in NS.

Results: Significant reduction in proteinuria[26,37]



Madan et al, 2016 publication outcome*[26]: reduction in proteinuria

Partial remission	60% (9/15)

Post hoc analysis outcome†[37]: remission outcome defined as reduction in proteinuria with stable or improved renal function

Partial remission	47% (7/15)

Renal function[37]

	Baseline	Post-Acthar Gel
Mean serum creatinine‡	2.27 mg/dL	2.58 mg/dL

‡Calculation based on patients who had reported pre- and post-Acthar Gel values. Does not include 1 patient who terminated early due to AEs.

Outcome Measures

***Treatment outcome definitions from Madan et al, 2016 publication.** Complete remission: final proteinuria <500 mg/day, and partial remission: ≥50% reduction in proteinuria from baseline and final proteinuria 500-3500 mg/day, with examination of preserved or improved renal function as indicated by serum creatinine that does not worsen >25% from baseline.

†**Treatment outcome definitions from the post hoc analysis.** A post hoc analysis 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 ≤125% of baseline or eGFR ≥75% of baseline).

KDIGO=Kidney Disease: Improving Global Outcomes.

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.

In prospectively evaluated treatment-resistant patients with FSGS in the native kidney

Impact of Acthar Gel on proteinuria reduction

Overview[30]

Results are from a prospective, open-label, observational study of the safety and efficacy of 6 months of Acthar Gel in 22 patients with treatment-resistant NS, 13 of whom had FSGS. Patients were given Acthar Gel for 6 months.

- Only monotherapy results are presented for the 13 FSGS patients
- These 13 patients received Acthar Gel 40-80 units 2 to 3 times per week for 6 months

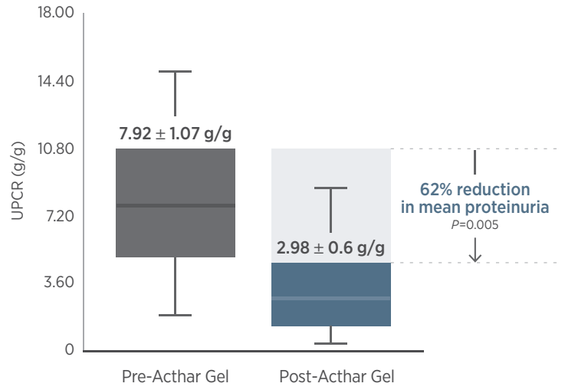
Patient characteristics[30]

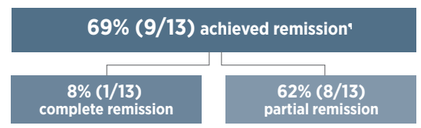
Mean baseline proteinuria	7.92 ± 1.07 g/g
Mean baseline eGFR	47 ± 6.8 mL/min/1.73 m^2
Baseline level of interstitial fibrosis	25% ± 0.05%

Prior treatment history‖	At least 92% of patients received prior IST
Mean disease duration prior to Acthar Gel	19 ± 6.1 months

‖Majority included steroids and CNI, but also included MMF and rapamycin alone or in combination.
Other than steroids, listed therapies are not approved for the reduction of proteinuria in NS.

Assessment after 6 months of Acthar Gel monotherapy[30]





¶Complete remission: UPCR <300 mg/g. Partial remission: 50% reduction in UPCR to <3500 mg/g.

Study limitations

Results of this study are limited by small sample size, lack of power, and variable dosing regimens and may not be fully representative of outcomes in the overall patient population. Acthar Gel has not been formally studied as a combination therapy with other treatments and is not indicated to reduce proteinuria in patients with diabetic nephropathy. There was no comparison group for interpretation of safety and efficacy findings with Acthar Gel. Patients were previously treated with other therapies and the clinical outcomes may not be solely attributable to Acthar Gel.

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® GEL
(repository corticotropin injection) 80 U/mL

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*[31]

Overview[31]

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[31,36]

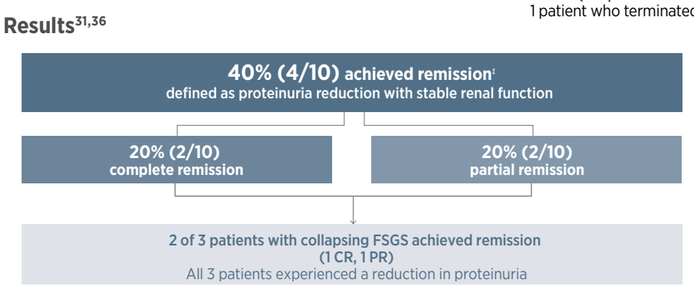
Baseline proteinuria	3100-36,000 mg/g; 5.8-8.43 g/day
Mean baseline serum creatinine‡	2.22 mg/dL
FSGS variants	Collapsing (n=3) Tip (n=1) Not otherwise specified (n=2) Not further categorized (n=4)
Prior treatment history†	50% of patients (5/10) received ≥2 IST
Median disease duration prior to Acthar Gel	42 months

†Steroids, MMF, abatacept, CTX, cyclosporine, azathioprine, pentoxifylline, and/or tacrolimus used either alone or in combination.

Other than steroids, listed therapies are not approved for the reduction of proteinuria in NS.

‡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.

Results[31,36]



*Complete remission: final proteinuria as measured by 24-hour urine protein <500 mg/day or spot urine protein <500 mg/g creatinine; >50% reduction from baseline; with stable renal function (rise in serum creatinine <25%). Partial remission: final proteinuria <3500 mg/day or <3500 mg/g of creatinine; >50% proteinuria reduction from baseline; with stable renal function.

Renal function[36]

	Baseline	Post-Acthar Gel
Mean serum creatinine§	2.22 mg/dL	2.12 mg/dL

§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.

Study limitations

The results may not be fully representative of outcomes in the overall patient population. There was no comparison group for interpretation of safety and efficacy findings with Acthar Gel. 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.

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, biopsy-proven FSGS in the native kidney

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

In a combined prospective trial and retrospective review, 29% of patients (7/24) achieved remission defined as proteinuria reduction with stable renal function‖[35]

Overview[35]

Patients with FSGS (n=24) were treated with Acthar Gel. Dosing regimens varied between the Columbia and Stanford Medical Center treatment sites.¶

¶This trial includes longer-term follow-up data for 4 patients from previous trials: 1 patient from the Bomback 2011 dataset and 3 patients from the Bomback 2012 trial.

Twelve patients were treated with the Stanford regimen: 40 units subcutaneously once per week for 2 weeks, 80 units subcutaneously once per week for 2 weeks, then 80 units subcutaneously twice weekly to complete 16 weeks of therapy. Seven patients treated with the Columbia regimen were prescribed 40 units subcutaneously twice weekly for 2 weeks, followed by 80 units subcutaneously twice weekly for a duration of 24 weeks. The remaining 5 patients who were also treated at Columbia received Acthar Gel at regimens prescribed at the discretion of the treating physician, with a median regimen of 80 units subcutaneously twice weekly. Duration of therapy ranged from 12 to 56 weeks.

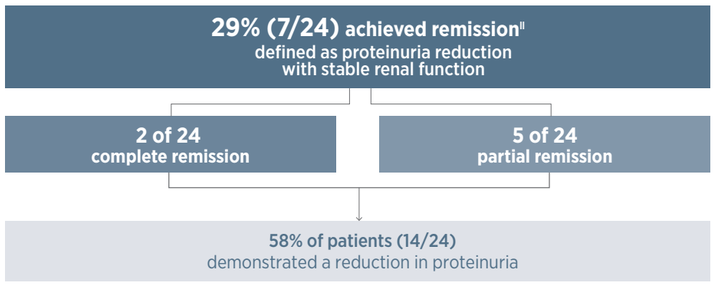
Patient characteristics[35]

Median baseline proteinuria	4595 mg/g (IQR: 2200-8020)
Median baseline serum creatinine	2.0 mg/dL (IQR: 1.1-2.7)
Median baseline eGFR	36 mL/min/1.73 m^2 (IQR: 28-78)
Median baseline albumin	2.9 g/dL (IQR: 2.0-3.6)
Prior treatment history#	92% of patients (22/24) received ≥1 prior IST
Disease duration prior to Acthar Gel	34 months

#IST included steroids, cyclosporine, MMF, CTX, and/or tacrolimus used either alone or in combination.

Other than steroids, listed therapies are not approved for the reduction of proteinuria in NS.

Acthar Gel helped patients achieve remission‖[35]



‖Complete remission: stable or improved renal function with final proteinuria falling to <500 mg/g by spot UPCR or 24-hour urine protein measurement. Partial remission: stable or improved renal function with ≥50% reduction in proteinuria and final proteinuria 500-3500 mg/g.

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.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

Across multiple datasets of patients with FSGS in the native kidney

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

Type of dataset	Retrospective case series (n=15)[26] [Madan et al, 2016]	Prospective, observational study* (N=22; n=13)[30] [Tumlin et al, 2017]	Retrospective case series (n=10)[31] [Filippone et al, 2016]	Combined prospective trial and retrospective review (n=24)†[35] [Hogan et al, 2013]
Adverse events	Hyperglycemia (n=2) Swelling (n=1) Hypertension (n=1) Weight gain (n=1) Upper respiratory tract infection (n=1)	Hyperglycemia (n=5) Edema (n=3) Insomnia (n=2)	Weight gain (n=4) Hypertension (n=2) Increased skin pigmentation (n=2) Myalgia (n=2) Worsening diabetes (n=2) Weakness (n=1) Cushingoid features (n=1) Edema (n=1) Fatigue (n=1)	• 52 adverse events were reported in 21 patients on Acthar Gel • 23 corticosteroid-like adverse events; the most common included: – Swelling, edema, volume overload, weight gain (n=5) – Increased energy (n=4) – Change in mood (n=4)
Early termination	Edema (n=1) Reasons not given (n=1)	n=0	Myalgia, weight gain, and worsening diabetes (n=1) Edema and hypertension (n=1)	New-onset diabetes (n=1)

*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 MCD): 1 patient from the Bomback 2011 dataset and 3 patients from the Bomback 2012 trial.

- Across multiple FSGS datasets, adverse events were considered tolerable with nearly 90% of patients completing the full prescribed course of Acthar Gel[26,30,31,35]
  - 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=1)[26,31,35]

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

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 (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
- 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
- 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, Cushingoid symptoms, constipation, diarrhea, 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.
Please see the accompanying full Prescribing Information.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

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*This research was supported and/or funded by a grant from Mallinckrodt Pharmaceuticals.

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 hyperactive immune cells during active disease and stimulates low levels of cortisol release[14,18,19,24]

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 renal function status[4,32]
- 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[4,32]
- 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 renal function status[26-28,30,31,35]
- In the datasets presented, 29%-69% of patients taking Acthar Gel experienced reductions in proteinuria to remission levels with stable or improved renal function[26-28,30,31,35]
  - Four out of five studies included stable or improved renal function as part of the definition of remission[26-28,31,35]
- 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[34]
  - In Acthar Gel clinical datasets, the most common Acthar Gel dosing regimen was 80 units subcutaneously twice weekly for 6 months[26-31,35]

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 (e.g. trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA suppression after stopping treatment

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

Mallinckrodt Pharmaceuticals

Acthar® GEL
(repository corticotropin injection) 80 U/mL

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 | SUBCUTANEOUS use
Initial U.S. Approval: 1952

----------INDICATIONS AND USAGE ----------
- Acthar Gel is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age. (1.1)
- Acthar Gel is indicated for the treatment of exacerbations of multiple sclerosis in adults. (1.2)
- Acthar Gel may be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state. (1.3 to 1.9)

---------- DOSAGE AND ADMINISTRATION ----------
- In the treatment of infantile spasms, the recommended dose is 150 U/m^2 divided into twice daily intramuscular injections of 75 U/m^2. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period. (2.1)
- In the treatment of acute exacerbations of multiple sclerosis, daily intramuscular or subcutaneous doses of 80-120 units for 2-3 weeks may be administered. It may be necessary to taper the dose. (2.2)
- In the treatment of other disorders and diseases, dosing will need to be individualized depending on the disease under treatment and the medical condition of the patient. It may be necessary to taper the dose. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------
- 5 mL multi-dose vial containing 80 USP units per mL. (3)

----------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.
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel.
- Acthar Gel is contraindicated in children under 2 years of age with suspected congenital infections. (4)
- Treatment of conditions listed within the INDICATIONS AND USAGE section is contraindicated when they are accompanied by primary adrenocortical insufficiency or adrenocortical hyperfunction. (4)

----------WARNINGS AND PRECAUTIONS ----------
- Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination or reactivation of latent infections. Signs and symptoms of infection may be masked. (5.1)
- Adrenal Insufficiency after Prolonged Therapy: Monitor for effects of hypothalamic-pituitary-axis suppression after stopping treatment. (5.2)
- Cushing's Syndrome: May occur after prolonged therapy. Monitor for signs and symptoms. (5.2)
- Elevated Blood Pressure, Salt and Water Retention and Hypokalemia: Monitor blood pressure and sodium and potassium levels. (5.3)
- Vaccination: Do not administer live or live attenuated vaccines to patients on immunosuppressive doses. (5.4)
- Masking of Symptoms of Other Underlying Disease/Disorders. Monitor patients for signs of other underlying disease/disorders that may be masked. (5.5)
- Gastrointestinal Perforation and Bleeding: There is a risk for gastric ulcers and bleeding. There is an increased risk of perforation in patients with certain GI disorders. Signs and symptoms may be masked. Monitor for signs of perforation and bleeding. (5.6)
- Behavioral and Mood Disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression and psychosis. Existing conditions may be aggravated. (5.7)
- Comorbid Diseases: Symptoms of diabetes and myasthenia gravis may be worsened with treatment. (5.8)
- Ophthalmic Effects: Monitor for cataracts, infections and glaucoma. (5.9)
- Immunogenicity Potential: Neutralizing antibodies with chronic administration may lead to a loss of endogenous ACTH activity. (5.10)
- Use in Patients with Hypothyroidism or Liver Cirrhosis: May result in an enhanced effect. (5.11)
- Negative Effects on Growth and Physical Development: Monitor pediatric patients on long term therapy. (5.12)
- Decrease in Bone Density: Monitor for osteoporosis in patients on long term therapy. (5.13)
- Use in Pregnancy: Embryocidal effect. Apprise women of potential harm to the fetus. (5.14)

----------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)
- Specific adverse reactions resulting from drug use in children under 2 years of age are increased risk of infections, hypertension, irritability, Cushingoid symptoms, cardiac hypertrophy and weight gain. (6.1.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt at 1-800-778-7898 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS----------
- Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy. (7)

----------USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Acthar Gel 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. (8.1)
- Pediatric Use: Prolonged use of Acthar Gel in children may inhibit skeletal growth. If use is necessary, it should be given intermittently with careful observation. (5.12 and 8.4)

See 17 for Patient Counseling Information and FDA-approved Medication Guide

Revised: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Infantile spasms
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 it affects 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 DOSAGE AND ADMINISTRATION

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/m^2 (divided into twice daily intramuscular injections of 75 U/m^2) 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/m^2 in the morning for 3 days; 15 U/m^2 in the morning for 3 days; 10 U/m^2 in the morning for 3 days; and 10 U/m^2 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

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

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
Acthar Gel may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic infections. Patients with latent tuberculosis or tuberculin 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.

Signs or symptoms 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 characteristics sites (e.g., moon face, truncal obesity), cutaneous striae, easy bruisability, 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 impending 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 Ophthalmic 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 fungi 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.

5.12 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

System Organ Class	Recommended 75 U/m² bid n=122, (%)	150 U/m² qd n=37 (%)
Cardiac disorders		
Cardiac Hypertrophy	3	0
Endocrine disorders		
Cushingoid	3	22
Gastrointestinal disorders		
Constipation	0	5
Diarrhea	3	14
Vomiting	3	5
General disorders and administration site conditions		
Irritability	7	19
Pyrexia	5	8
Infections and infestations		
Infection*	20	46
Investigations		
Weight gain	1	3
Metabolism and nutrition disorders		
Increased appetite	0	5
Decreased appetite	3	3
Nervous system disorders		
Convulsion†	12	3
Respiratory, thoracic and mediastinal disorders		
Nasal Congestion	1	5
Skin and subcutaneous tissue disorders		
Acne	0	14
Rash	0	8
Vascular disorders		
Hypertension	11	19

* 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
Hypokalemic alkalosis (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 interpreter 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, has 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 m^2 would be 60 U/day. Using the 1-cc syringe supplied with Acthar Gel, the maximum amount that can be injected is 80 U/injection, 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 low 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% 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 weakly androgenic substances. Prolonged administration of large doses of Acthar Gel induces 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/m^2 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/m^2 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

Caretakers 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 or fever 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 (5.3) and Adverse Reactions (6.1.1)]*.

Patients, their caregivers and families should be advised that if the patient or the caregiver notices blood or a change in color of the patient's stool they should contact their physician *[see Warnings and Precautions (5.6)]*.

Caregivers and families of infants and children treated with Acthar Gel should be informed that the patient may show signs of irritability and sleep disturbances. These effects are reversible once Acthar Gel therapy is stopped *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1.1)]*.

Patients, their caregivers and families should be advised that changes in appetite, most often leading to weight gain, are seen with Acthar Gel therapy, becoming more frequent as the dose or treatment period increases. These effects are reversible once Acthar Gel therapy is stopped *[see Warnings and Precautions (5.12) 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), and (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 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 *[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)]*.

Manufactured for:
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