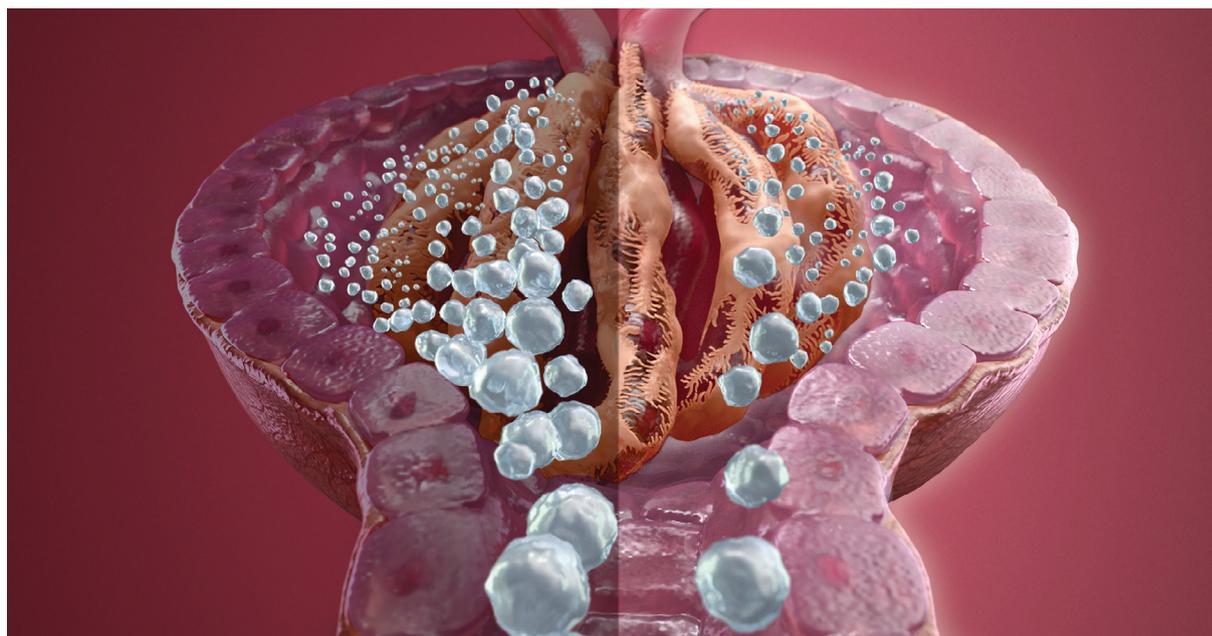


# Retrospective case series of Acthar treatment for proteinuria in 44 patients with various etiologies of nephrotic syndrome

Largest-to-date Acthar clinical experience in a majority of patients who received previous therapies

## Acthar Gel in the Treatment of Nephrotic Syndrome: a Multicenter Retrospective Case Series

Arvind Madan, Snezana Mijovic-Das, Ana Stankovic, Geoffrey Teehan, Amber S. Milward, Anupa Khastgir. *BMC Nephrology*. 2016;17:37.



This retrospective case series is the largest-to-date clinical experience with Acthar, an FDA-approved naturally sourced complex mixture of adrenocorticotrophic hormone analogs and other pituitary peptides, for the reduction of proteinuria associated with various etiologies of nephrotic syndrome.

Presentation of study design, baseline characteristics, efficacy, and safety findings within this summary 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 based on a compound primary outcome measure that included both reduction in proteinuria and stable or improved renal function (creatinine  $\leq 125\%$  of baseline or eGFR  $\geq 75\%$  of baseline). This compound outcome measure aligns with the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommendations for assessing treatment response to nephrotic syndrome therapy.

The original research was performed under a grant from Mallinckrodt. The post hoc analysis, using the compound outcome measure for response, was reviewed and approved by the primary and senior authors of the original paper. All data needed to perform the analysis were presented in the original paper.

### 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 7.

Please see the accompanying full Prescribing Information.

**Acthar**<sup>®</sup>GEL  
(repository corticotropin injection) 80 U/mL

# Retrospective case series of Acthar gel treatment for proteinuria in 44 patients with various etiologies of nephrotic syndrome

## Overview<sup>1</sup>

A multicenter retrospective review of 44 patients with various nephrotic syndrome (NS) etiologies examined the efficacy and safety of Acthar for the reduction of proteinuria. The majority (30/44) had received ≥1 previous cytotoxic or immunosuppressive therapy. The remaining 14 patients were treatment naïve.

Patients ≥18 years diagnosed with NS received Acthar treatment for ≥6 months and had an assessment of either 24-hour proteinuria level (mg/d) or UPCR (g/g converted to mg/d) prior to and following 6 months of Acthar therapy. Patients did not have to meet a prespecified level of proteinuria at baseline to be included in the study.

Cases included 44 patients across the following NS etiologies:

Etiology	Number of Patients
<b>Focal Segmental Glomerulosclerosis (FSGS)</b>	<b>15</b>
<b>Idiopathic Membranous Nephropathy (iMN)</b>	<b>11</b>
<b>IgA Nephropathy (IgAN)</b>	<b>5</b>
<b>Systemic Lupus Erythematosus Class V Membranous Lupus Nephritis (MLN)</b>	<b>2</b>
<b>Minimal Change Disease (MCD)</b>	<b>2</b>
<b>Membranoproliferative Glomerulonephritis (MPGN)</b>	<b>1</b>
<b>Fibrillary Glomerulonephritis (FGN)</b>	<b>1</b>
<b>Unbiopsied NS (UNS)</b>	<b>3</b>
Diabetic Nephropathy* (DN)	4

\*Individual results of the 4 patients with DN are not included in this presentation. Acthar is not indicated to reduce proteinuria associated with DN.

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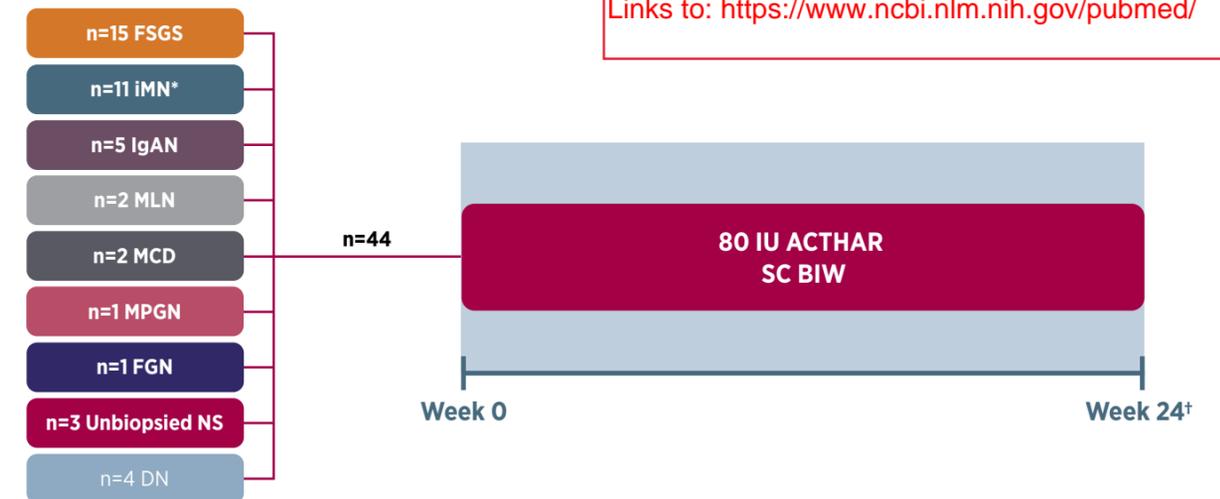


You may find more information about this study at **BMC Nephrology** or at **PubMed.gov**.

Links to: <https://bmcnephrol.biomedcentral.com/>

Links to: <https://www.ncbi.nlm.nih.gov/pubmed/>

## Design<sup>1</sup>



\*One patient with iMN was treated with Acthar 40 IU.

†Patients were prescribed Acthar for a minimum of 24 weeks; actual treatment durations varied.

Acthar dosing regimen and concomitant medications, including angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and immunosuppressive and cytotoxic drugs, were documented.

Dosing of Acthar (as stated in Prescribing Information): Dosage and frequency of Acthar should be individualized according to the medical condition, severity of the disease, and initial response of the patient.

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

## Outcome Measures<sup>1</sup>

Outcome measures evaluated in the case series included:

- Responses that were defined as:
  - Complete Remission (CR): stable or improved renal function (serum creatinine that did not worsen >25% from baseline) and final proteinuria <500 mg/d
  - Partial Remission (PR): stable or improved renal function (serum creatinine that did not worsen >25% from baseline) with ≥50% reduction in proteinuria from baseline and final proteinuria 500–3500 mg/d
  - Clinical Response (CL): ≥30% reduction in proteinuria from baseline that did not meet CR or PR criteria
  - No Response (NR): patients showing no response failed to meet remission or CL criteria

- Frequency of adverse events and early discontinuation due to adverse events

Additional laboratory measures included change in serum creatinine, albumin, and total cholesterol if data were available.

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### Patient Baseline Characteristics<sup>1</sup>

Among the 44 patients, the majority (30/44; 68.2%) had received ≥1 prior immunosuppressive or cytotoxic therapy and 20 of 44 (45.5%) had received ≥2 prior immunosuppressive and/or cytotoxic treatments.

Etiology	Previously Used IST or CT (n/N)
FSGS	12/15
iMN	10/11
IgAN	1/5
MLN	2/2
MCD	2/2
MPGN	0/1
FGN	1/1
Unbiopsied NS	2/3
DN	0/4

**68.2% of patients (n=30/44) were previously treated with ≥1 of the following:**

- steroids
- mycophenolate mofetil
- cyclosporine
- cyclophosphamide
- tacrolimus
- azathioprine
- methotrexate
- chlorambucil
- rituximab

**31.8% of patients (n=14/44) received no previous IST/CT**

IST=immunosuppressive therapy. CT=cytotoxic therapy.

### Patient Baseline Characteristics<sup>1</sup> (continued)

Characteristics of patients by NS etiology group are presented below. Over half of patients (26/44; 59.1%) showed impaired renal function prior to Acthar treatment.

Etiology	(n)	Age±SD (years)	Serum Albumin* (g/dL)	Serum Creatinine* (mg/dL)	Proteinuria* (mg/d)	Median Proteinuria* (mg/d)
FSGS	15	53.3±12.9	1.7–3.9	0.9–4.8	2500–9306	5000
iMN	11	53.6±18.9	1.4–3.9	0.9–3.3	1930–15,400	5210
IgAN	5	35.0±8.4	3.0–4.0	1.0–2.8	2230–10,000	2674
MLN	2	37.5±4.9	1.7–1.8	1.0	8000–19,890	13,945
MCD	2	33.5±13.4	2.1–3.7	0.9–1.0	2000–15,000	8500
MPGN	1	22.0	1.5	0.7	10,000	10,000
FGN	1	63.0	1.4	5.6	13,000	13,000
Unbiopsied NS	3	55.7±6.1	3.1–3.5	1.3–1.7	3000–5500	4500
DN	4	54.0±19.9	2.0–3.4	1.9–4.8	11,000–25,000	15,785

\*Values based on patients for whom data were available.

\*Median proteinuria adapted from reported proteinuria values given for each patient.

### 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 7.  
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### SELECT IMPORTANT SAFETY INFORMATION

#### Warnings and Precautions (cont.)

- 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

Please see additional Important Safety Information throughout and on page 7.  
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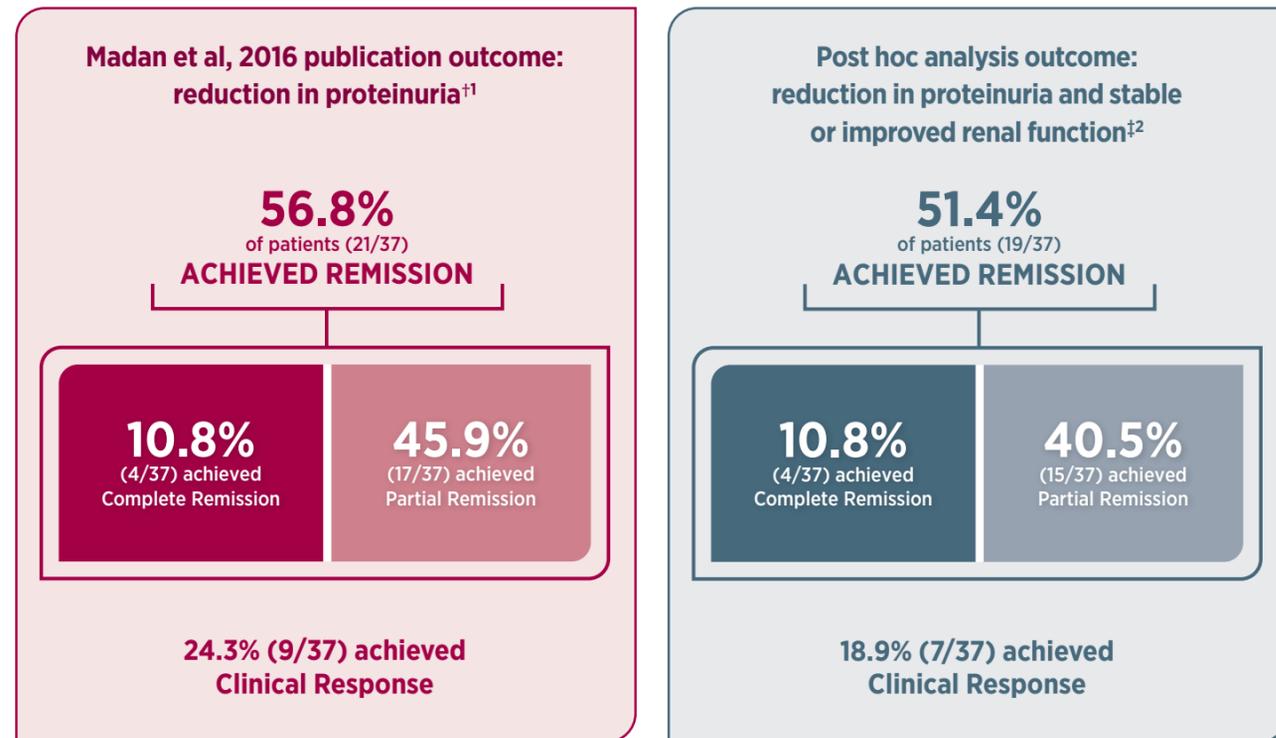
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## Results<sup>1</sup>

There was significant proteinuria reduction from baseline to post-Acthar treatment for patients with pre- and post-Acthar proteinuria values (n=40; mean reduction 3984.8±4069.1 mg/d, P<0.0001).\*

\*Of the 44 patients, 4 patients did not have follow-up proteinuria values.

### Response rates from the 37 of 44 patients who completed Acthar treatment



## 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. Most patients were on multiple therapies. The clinical outcomes may not be solely attributable to Acthar. Of the 44 patients, 37 completed treatment and 7 terminated early.<sup>1,2</sup>

## Outcome Measures

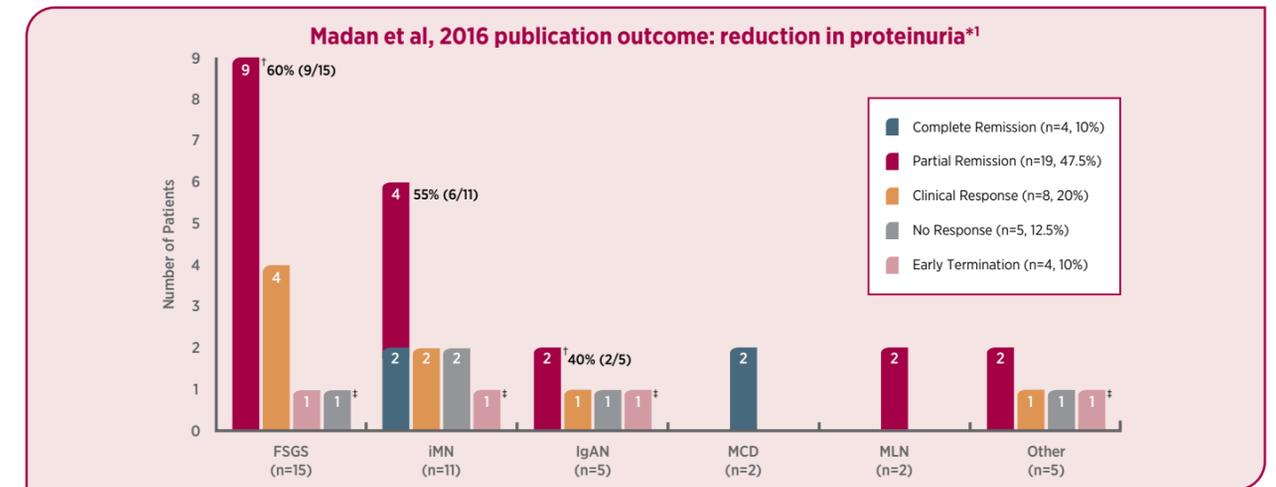
### <sup>†</sup>Treatment outcome definitions from Madan et al, 2016 publication<sup>1</sup>

Complete Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) and final proteinuria <500 mg/d. Partial Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) with ≥50% reduction in proteinuria from baseline and final proteinuria 500–3500 mg/d. Clinical Response=≥30% reduction in proteinuria from baseline that did not meet complete or partial remission criteria.

### <sup>‡</sup>Treatment outcome definitions from the post hoc analysis<sup>2</sup>

A post hoc analysis assessed treatment response to Acthar based on a compound primary outcome measure that included both reduction in proteinuria and stable or improved renal function (creatinine ≤125% of baseline or eGFR ≥75% of baseline).

## Treatment response rates across multiple etiologies of NS

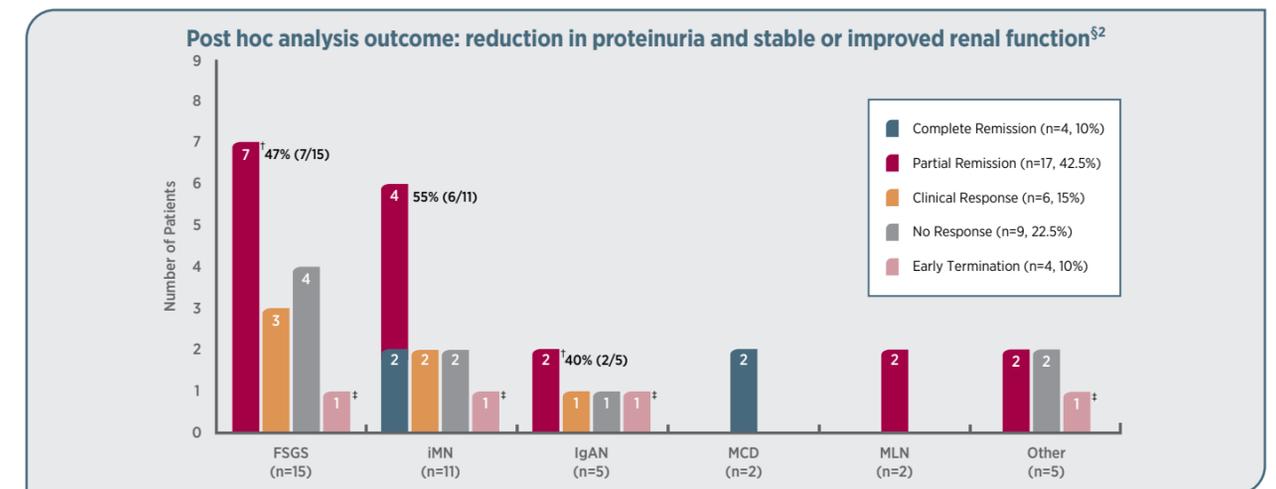


Adapted from Madan et al, 2016. Figure reports results for all patients (n=40). Results from 4 patients with DN are not included. Acthar is not indicated to reduce proteinuria associated with DN. Other includes 1 patient with MPGN, 1 patient with FGN, and 3 patients with unbiopsied NS.

\*Complete Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) and final proteinuria <500 mg/d. Partial Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) with ≥50% reduction in proteinuria from baseline and final proteinuria 500–3500 mg/d. Clinical Response=≥30% reduction in proteinuria from baseline that did not meet complete or partial remission criteria. No Response=patients showing no response failed to meet remission or clinical response criteria.<sup>1</sup>

<sup>†</sup>Includes patient who terminated early but had post-Acthar proteinuria assessment.

<sup>‡</sup>Includes patients who terminated early and did not have post-Acthar proteinuria assessment.



Adapted from Madan et al, 2016. Figure reports results for all patients (n=40). Results from 4 patients with DN are not included. Acthar is not indicated to reduce proteinuria associated with DN. Other includes 1 patient with MPGN, 1 patient with FGN, and 3 patients with unbiopsied NS.

<sup>§</sup>Complete remission, partial remission, and clinical response included both proteinuria reduction, as defined by Madan et al, and stable or improved renal function (serum creatinine that did not worsen >25% from baseline).<sup>2</sup>

## 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. Most patients were on multiple therapies. The clinical outcomes may not be solely attributable to Acthar.<sup>1,2</sup>

## SELECT IMPORTANT SAFETY INFORMATION

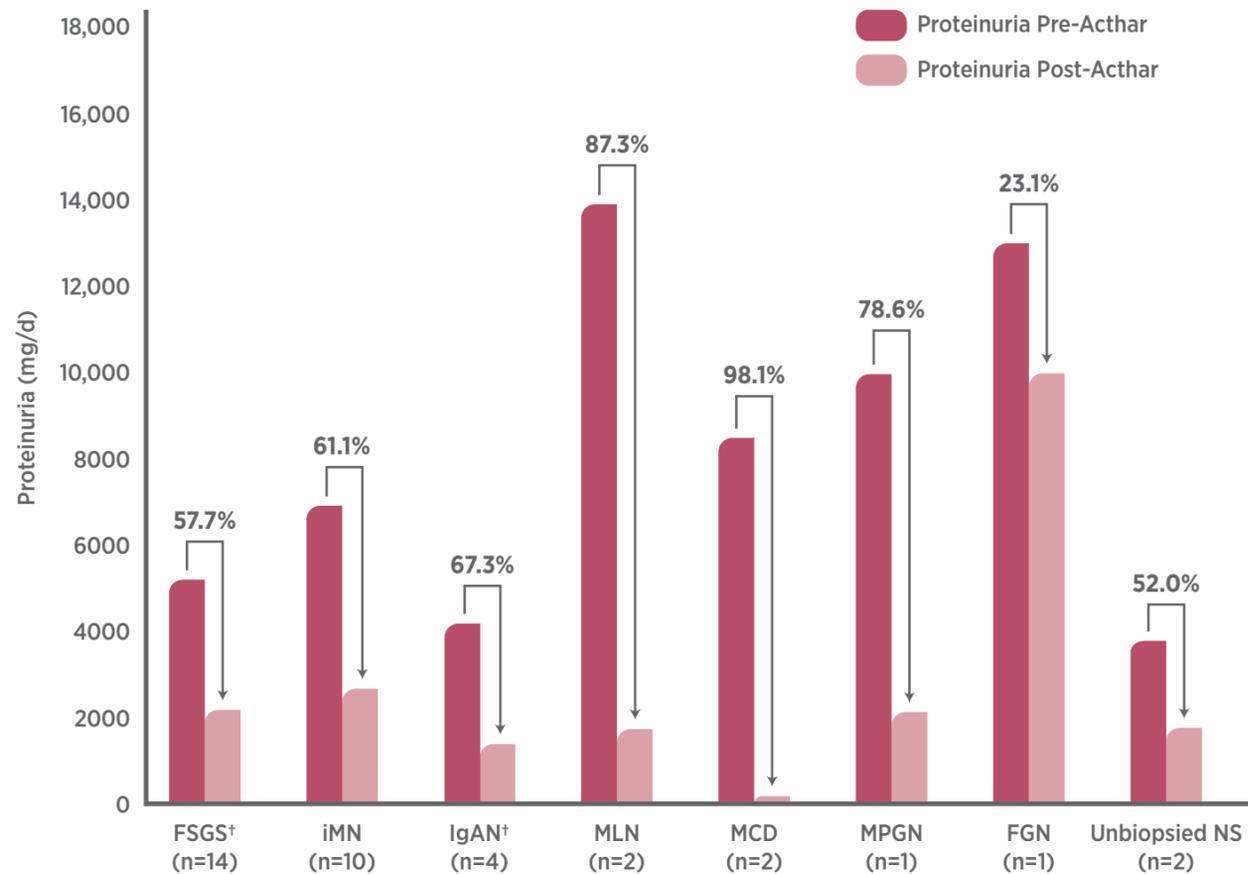
### Warnings and Precautions (cont.)

- 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

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## Changes in proteinuria levels from baseline across multiple etiologies of NS\*1



Adapted from Madan et al, 2016.

\*Figure includes all patients with post-Acthar proteinuria values, with the exception of 4 patients with DN (n=36).

†Includes a patient who terminated early but had post-Acthar proteinuria assessment.

## Study Limitations<sup>1,2</sup>

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/d. Most patients were on multiple therapies. The clinical outcomes may not be solely attributable to Acthar. Longer treatment duration and follow-up may be needed for meaningful treatment responses. The relapse rate following successful treatment with Acthar is not yet known.

## Safety Findings<sup>1</sup>

Adverse events during Acthar treatment were reported by 30% (13/44) of patients, and 16% (7/44) had early termination due to treatment-related adverse events. These results are summarized below.

Adverse Event	Number of Events	Reason for Early Termination	Number of Events
Weight gain	7	Weight gain	2
Hypertension	4	Hypertension	2
Hyperglycemia	4	Fatigue	1
Increased swelling	1	Edema	1
Fatigue	1	Seizures	1
Dizziness	1	Patient decision	1
Hypokalemia	1	Reason not given	1
Upper respiratory tract infection	1		
Seizures	1		
Decreased bone mineralization	1		

## SELECT IMPORTANT SAFETY INFORMATION

### Warnings and Precautions (cont.)

- 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

Please see additional Important Safety Information throughout and on page 7.

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## Individual FSGS Patient Results<sup>1</sup>

60% (9/15) of patients with FSGS achieved Partial Remission based on proteinuria reduction<sup>1</sup>

47% (7/15) of patients with FSGS achieved Partial Remission based on proteinuria reduction and stable or improved renal function<sup>2</sup>

Pt	Serum Albumin (g/dL)		Serum Creatinine (mg/dL)		Proteinuria (mg/d)		Proteinuria Change (%)	Outcome	
	Initial	Final	Initial	Final	Initial	Final		Proteinuria-Based Response*	Proteinuria- and Renal Function-Based Response <sup>†2</sup>
8	NA	NA	1.2	1.1	4000	765	-80.9	PR	PR
11	3.5	3.7	2.4	3.1	3500	750	-78.6	PR	NR
6	2.8	3.9	3.0	2.5	7500	1768	-76.4	PR	PR
12	3.8	4.0	1.5	1.2	5700	1500	-73.7	PR <sup>‡</sup>	X <sup>‡</sup>
4	3.9	4.0	4.8	6.7	7900	2300	-70.9	PR	NR
9	3.1	3.3	1.6	2.0	9306	2773	-70.2	PR	PR
2	3.0	3.4	0.9	0.8	5800	2016	-65.2	PR	PR
1	1.7	2.7	1.7	1.6	6700	3300	-50.7	PR	PR
14	3.7	NA	2.5	3.0	2500	1246	-50.2	PR	PR
10	NA	4.0	4.4	5.0	2830	1629	-42.4	CL	CL
13	3.2	3.5	3.1	4.1	3250	2073	-36.2	CL	NR
7	3.1	3.6	1.1	1.3	5280	3560	-32.6	CL	CL
3	3.2	3.8	2.2	2.2	5000	3422	-31.6	CL	CL
15	3.6	3.3	1.4	1.5	4070	3930	-3.4	NR	NR
5	3.2	NA	3.2	NA	3840	NA	NA	X	X

\*Complete Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) and final proteinuria <500 mg/d. Partial Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) with ≥50% reduction in proteinuria from baseline and final proteinuria 500–3500 mg/d. Clinical Response=≥30% reduction in proteinuria from baseline that did not meet complete or partial remission criteria. No Response=patients showing no response failed to meet remission or clinical response criteria.<sup>1</sup>

<sup>†</sup>Complete remission, partial remission, and clinical response included both proteinuria reduction, as defined by Madan et al, and stable or improved renal function (serum creatinine that did not worsen >25% from baseline).<sup>2</sup>

<sup>‡</sup>Patient demonstrated Partial Remission before terminating treatment early.

### SELECT IMPORTANT SAFETY INFORMATION

#### Warnings and Precautions (cont.)

- 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

Please see additional Important Safety Information throughout and on page 7.

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## Individual iMN Patient Results<sup>1</sup>

55% (6/11) of patients with iMN achieved Complete or Partial Remission based on proteinuria reduction<sup>1</sup>

55% (6/11) of patients with iMN achieved Complete or Partial Remission based on proteinuria reduction and stable or improved renal function<sup>2</sup>

Pt	Serum Albumin (g/dL)		Serum Creatinine (mg/dL)		Proteinuria (mg/d)		Proteinuria Change (%)	Outcome	
	Initial	Final	Initial	Final	Initial	Final		Proteinuria-Based Response*	Proteinuria- and Renal Function-Based Response <sup>†2</sup>
6	3.3	3.4	1.0	0.9	5500	349	-93.7	CR	CR
7	3.9	4.0	0.9	1.0	2400	163	-93.2	CR	CR
3	1.5	3.1	2.5	1.9	15,400	2376	-84.6	PR	PR
2	1.4	3.3	1.2	1.1	6354	1000	-84.3	PR	PR
10	3.5	3.7	1.3	1.6	5210	1780	-65.8	PR	PR
9	3.8	3.7	2.1	2.2	1930	728	-62.3	PR	PR
4	1.6	2.1	1.9	1.9	10,000	4000	-60.0	CL	CL
1	2.7	3.2	1.3	1.3	13,600	6600	-51.5	CL	CL
5	3.8	3.7	1.9	2.0	4000	3475	-13.1	NR	NR
11	NA	NA	3.3	3.8	5132	6600	28.6	NR	NR
8	3.2	NA	1.3	NA	3070	NA	NA	X	X

\*Complete Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) and final proteinuria <500 mg/d. Partial Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) with ≥50% reduction in proteinuria from baseline and final proteinuria 500–3500 mg/d. Clinical Response=≥30% reduction in proteinuria from baseline that did not meet complete or partial remission criteria. No Response=patients showing no response failed to meet remission or clinical response criteria.<sup>1</sup>

<sup>†</sup>Complete remission, partial remission, and clinical response included both proteinuria reduction, as defined by Madan et al, and stable or improved renal function (serum creatinine that did not worsen >25% from baseline).<sup>2</sup>

Acthar is indicated to reduce proteinuria of nephrotic syndrome. The impact of Acthar on other relevant lab values has not been more formally assessed and is included here for clinical context only.

Results are based on a retrospective case series of 44 patients and may not be fully representative of outcomes in the overall patient population. Most patients were on multiple therapies. The clinical outcomes may not be solely attributable to Acthar.<sup>1,2</sup>

CR	Complete Remission
PR	Partial Remission
CL	Clinical Response
NR	No Response
X	Early Termination

## Individual Patient Results for IgAN and Other Etiologies<sup>1</sup>

Pt	Etiology	Serum Albumin (g/dL)		Serum Creatinine (mg/dL)		Proteinuria (mg/d)		Proteinuria Change (%)	Outcome	
		Initial	Final	Initial	Final	Initial	Final		Proteinuria-Based Response*	Proteinuria- and Renal Function-Based Response <sup>†2</sup>
4	IgAN	3.0	4.0	1.0	1.0	10,000	800	-92.0	PR †	X †
5	IgAN	NA	4.2	1.3	1.3	2230	815	-63.5	PR	PR
2	IgAN	3.9	NA	1.4	1.5	2674	1700	-36.4	CL	CL
3	IgAN	4.0	3.6	1.3	1.3	2439	2360	-3.2	NR	NR
1	IgAN	3.9	NA	2.8	NA	4000	NA	NA	X	X
2	MLN	1.7	2.4	1.0	1.1	19,890	2454	-87.7	PR	PR
1	MLN	1.8	3.3	1.0	0.8	8000	1089	-86.4	PR	PR
2	MCD	2.1	2.3	1.0	0.7	15,000	89	-99.4	CR	CR
1	MCD	3.7	4.7	0.9	1.2	2000	241	-88.0	CR	CR
--	FGN	1.4	3.4	5.6	9.0	13,000	10,000	-23.1	NR	NR
--	MPGN	1.5	3.3	0.7	0.8	10,000	2141	-78.6	PR	PR
2	UNS	3.5	4.0	1.7	1.9	4500	2000	-55.6	PR	PR
1	UNS	3.5	4.6	1.6	2.2	3000	1600	-46.7	CL	NR
3	UNS	3.1	3.3	1.3	1.3	5500	NA	NA	X	X

\*Complete Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) and final proteinuria <500 mg/d. Partial Remission=stable or improved renal function (serum creatinine that did not worsen >25% from baseline) with ≥50% reduction in proteinuria from baseline and final proteinuria 500–3500 mg/d. Clinical Response=≥30% reduction in proteinuria from baseline that did not meet complete or partial remission criteria. No Response=patients showing no response failed to meet remission or clinical response criteria.<sup>1</sup>

<sup>†</sup>Complete remission, partial remission, and clinical response included both proteinuria reduction, as defined by Madan et al, and stable or improved renal function (serum creatinine that did not worsen >25% from baseline).<sup>2</sup>

<sup>‡</sup>Patient demonstrated Partial Remission before terminating treatment early.

**Acthar is indicated to reduce proteinuria of nephrotic syndrome. The impact of Acthar on other relevant lab values has not been more formally assessed and is included here for clinical context only.**

**Results are based on a retrospective case series of 44 patients and may not be fully representative of outcomes in the overall patient population. Most patients were on multiple therapies. The clinical outcomes may not be solely attributable to Acthar.<sup>1,2</sup>**

CR	Complete Remission
PR	Partial Remission
CL	Clinical Response
NR	No Response
X	Early Termination

## 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.**

**References:** 1. Madan A, Mijovic-Das S, Stankovic A, Teehan G, Milward AS, Khastgir A. Acthar gel in the treatment of nephrotic syndrome: a multicenter retrospective case series. *BMC Nephrol.* 2016;17:37. 2. Data on file: ARDUS/01-03/0917-0002. Mallinckrodt ARD, Inc.



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**Acthar<sup>®</sup>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 I 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<sup>2</sup> divided into twice daily intramuscular injections of 75 U/m<sup>2</sup>. 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. Advise 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](http://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

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### FULL PRESCRIBING INFORMATION

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

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

#### 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

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 characteristic 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  $\geq$  2% of Acthar Gel (repository corticotropin injection) Infants and Children under 2 years of Age**

System Organ Class	Recommended 75 U/m <sup>2</sup> bid n=122, (%)	150 U/m <sup>2</sup> qd n=37 (%)
<b>Cardiac disorders</b>		
Cardiac Hypertrophy	3	0
<b>Endocrine disorders</b>		
Cushingoid	3	22
<b>Gastrointestinal disorders</b>		
Constipation	0	5
Diarrhea	3	14
Vomiting	3	5
<b>General disorders and administration site conditions</b>		
Irritability	7	19
Pyrexia	5	8
<b>Infections and infestations</b>		
Infection*	20	46
<b>Investigations</b>		
Weight gain	1	3
<b>Metabolism and nutrition disorders</b>		
Increased appetite	0	5
Decreased appetite	3	3
<b>Nervous system disorders</b>		
Convulsion <sup>†</sup>	12	3
<b>Respiratory, thoracic and mediastinal disorders</b>		
Nasal Congestion	1	5
<b>Skin and subcutaneous tissue disorders</b>		
Acne	0	14
Rash	0	8

System Organ Class	Recommended 75 U/m <sup>2</sup> bid n=122, (%)	150 U/m <sup>2</sup> qd n=37 (%)
<b>Vascular disorders</b>		
Hypertension	11	19

\* Specific infections that occurred at  $\geq$  2% were candidiasis, otitis media, pneumonia and upper respiratory tract infections. <sup>†</sup> 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<sup>2</sup> 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 of 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<sup>2</sup> 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<sup>2</sup> 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)].

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