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

Dear Fellow Healthcare Provider,

I have prescribed Acthar Gel for the patient below to treat the ocular inflammatory disease affecting our patient. My intent in prescribing this therapy is not to affect other treatments or conditions outside the eye; however, I wanted you to be aware.

Patient Name: _____ Eye Condition: _____

Relevant Treatment History: _____

Physician Notes and Relevant Clinical Information: _____

Physician Name and Contact Information: _____

INDICATION

Acthar Gel is indicated for 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.

Acthar Product Description

- Acthar is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH) (1-39) analogs and other pituitary peptides.[1]
- Acthar is not ACTH; it has its own characterization, and is NOT interchangeable with any other ACTH products, including any approved in the US for diagnostic use only.[1,2]

Potential Mechanism of Action (MOA)

- Acthar engages melanocortin receptors (MCRs) expressed on immune, organ, and tissue cells throughout the body and is thought to produce both an indirect anti-inflammatory effect and a direct cell-modulation effect.[3-7]

The exact mechanism of action of Acthar Gel requires further investigation. This information is based on nonclinical and pharmacodynamic data, and the relationship to clinical benefit is unknown.

Clinical Efficacy

Uveitis Retrospective Review: Nelson WW, et al. *J Ocul Pharmacol Ther.* 2019;35(3):182-188.

In a retrospective chart-review study of the efficacy of Acthar in 91 patients with uveitis, the majority were previously treated with 2-3 medications:

- Physicians reported improved patient status* in 84% (n=76) of patients after Acthar therapy. Reported patient status remained the same in 16% (n=15) of patients.[8]
- 86% (n=78) of patients showed improvement in vision.[8]

Study limitations[8]

- Outcomes may be influenced by therapies not documented.
- Patient outcomes and safety were not quantified; physician assessment of patient outcomes may be subjective.
- Most patients were on multiple therapies; the clinical outcomes may not be solely attributable to Acthar Gel.

*Based on physicians' responses to the following two prompts:
- "What is the patient's current status?"
- "Please select the outcomes that have improved as a result of treatment with Acthar Gel."

Keratitis Phase 4 Study: Wirta D, et al. *Ophthalmol Ther.* 2021; 10(4):1077-1092.

In a phase 4, multicenter, open-label study of the efficacy and safety of Acthar Gel in 36* adult patients with treatment-resistant, refractory, severe, non-infectious keratitis, patients received 80 units of Acthar Gel twice weekly for 12 weeks, followed by a taper period of 4 weeks[9]:

- After 12 weeks of treatment with Acthar Gel, 50% (n=17) of patients† acheived the primary endpoint of clinically important improvement of ≥12 points in the IDEEL-symptom bother score.[9]
- After 12 weeks of treatment with Acthar Gel, 50%‡ of patients experienced ≥20% improvement; 44.1%§ of patients experienced ≥30% improvement and 14.7%¶ of patients experienced ≥50% improvement.

Safety findings[9]

- 33% (n=12) of patients experienced ≥1 TEAE; most TEAEs were single incidences.
- No new safety signals were identified.

Study limitations[9]

- Sample bias may exist as this was an open-label study, and patients were aware that they were receiving Acthar Gel.
- There was a relatively small sample size with a short treatment period of 12 weeks.
- The reported outcomes cannot be solely attributed to Acthar Gel. There is no control arm in this study, and other concomitant medications may not have been reported.

*A target sample size of 36 patients was determined empirically. All 36 patients were included in the safety group. Efficacy endpoints were analyzed in the modified intent-to-treat (mITT) population (n=35), defined as all patients who received at least one dose of Acthar Gel and who contributed any post-baseline efficacy data to the study.

†Data related to the IDEEL-symptom bother score were reported for 34 patients.
‡95% CI: 33.2%, 66.8%.
§95% CI: 27.4%, 60.8%.
¶95% CI: 2.8%, 26.5%.

Abbreviations: CI=confidence interval; IDEEL=Impact of Dry Eye on Everyday Life; mITT=modified intent-to-treat; TEAE=treatment-emergent adverse event.

SELECT IMPORTANT SAFETY INFORMATION

Contraindications

Acthar is contraindicated:

- For intravenous administration
- In infants under 2 years of age who have suspected congenital infections
- With concomitant administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of Acthar
- 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 on next page and full Prescribing Information at https://www.actharhcp.com/Static/pdf/Acthar-PI.pdf.

IMPORTANT SAFETY INFORMATION (cont'd)

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 axis 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. Monitor blood pressure and sodium and potassium levels
- 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 gastrointestinal (GI) bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain GI disorders. Monitor for signs of perforation and 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. Cases of anaphylaxis have been reported in the postmarketing setting. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH and Acthar activity
- There may be 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 in patients on long-term therapy

Adverse Reactions

- Commonly reported postmarketing adverse reactions for Acthar include injection site reaction, asthenic conditions (including fatigue, malaise, asthenia, and lethargy), fluid retention (including peripheral swelling), insomnia, headache, and blood glucose increased
- The most common adverse reactions for the treatment of infantile spasms (IS) are increased risk of infections, convulsions, hypertension, irritability, and pyrexia. Some patients with IS progress to other forms of seizures; IS sometimes masks these seizures, which may become visible once the clinical spasms from IS resolve

Pregnancy

- Acthar may cause fetal harm when administered to a pregnant woman

Please see full Prescribing Information at https://www.actharhcp.com/Static/pdf/Acthar-PI.pdf.

REFERENCES:

1. Acthar® Gel (repository corticotropin injection) [prescribing information]. Bedminster, NJ: Mallinckrodt ARD LLC. **2.** Cortrosyn® [package insert]. Rancho Cucamonga, CA: Amphastar Pharmaceuticals, Inc; 2010. **3.** Wright D, Fitch R. Acthar® Gel (repository corticotropin injection) enhances remyelination after cuprizone-induced demyelination [CMSC abstract NDM04]. *Int J MS Care*. 2019a;21(suppl 1):61-62. **4.** Olsen NJ, Decker DA, Higgins P, Becker PM, McAloose CA, Benko AL, Kovacs WJ. Direct effects of HP Acthar Gel on human B lymphocyte activation in vitro. *Arthritis Res Ther*. 2015;17:300. **5.** Catania A, Lonati C, Sordi A, Carlin A, Leonardi P, Gatti S. The melanocortin system in control of inflammation. *ScientificWorldJournal*. 2010;10:1840-1853. **6.** Healy LM, Lin YH, Jang JH, Rao V, Antel JP, Wright D. Melanocortin receptor mediated anti-inflammatory effect of repository corticotropin injection on human monocyte derived macrophages [ECTRIMS-ACTRIMS abstract EP1481]. *Mult Scler*. 2017;23:(S3):777. **7.** Wright D, Zweifel B, Prabha S, Galen K, Fitch R. Reduced steroidogenic activity of repository corticotropin injection induces a distinct cytokine response following T cell activation [EULAR abstract AB0082]. *Ann Rheum Dis*. 2019b;78 (suppl 2):1504. **8.** Nelson WW, Lima AF, Kranyak J, Opong-Owusu B, Ciepielewska G, Gallagher JR, Heap K, Carroll S. Retrospective medical record review to describe use of repository corticotropin injection among patients with uveitis in the United States. *J Ocul Pharmacol Ther*. 2019;35(3):182-188. **9.** Wirta D, McLaurin E, Ousler G, Liu J, Kacmaz RO, Grieco J. Repository corticotropin injection (Acthar Gel) for refractory severe non-infectious keratitis: efficacy and safety from a phase 4, multicenter, open-label study. *Ophthalmol Ther*. 2021;10(4):1077-1092.

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