Dear Healthcare Professional,

Thank you for your unsolicited request for information. Accompanying this letter is the following information you requested on Purified Cortrophin® Gel. If we can be of any further assistance, please contact our Medical Information department at (844) CORT-GEL (844-267-8435) between the hours of 9:00 AM to 7:00 PM ET (6:00 AM to 4:00 PM PT), Monday through Friday or via email at cortrophinmedinfo@anipharmaceuticals.com.

Purified Cortrophin Gel is indicated in the following disorders:

1. 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.
- Acute gouty arthritis.

2. Collagen diseases:
During an exacerbation or as maintenance therapy in selected cases of:
- Systemic lupus erythematosus.
- Systemic dermatomyositis (polymyositis).

3. Dermatologic diseases:
Severe erythema multiforme (Stevens-Johnson syndrome).
Severe psoriasis.

4. Allergic states:
Atopic dermatitis
Serum sickness.

5. Ophthalmic diseases:
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
- Allergic conjunctivitis.
- Keratitis.
- Iritis and iridocyclitis.
- Diffuse posterior uveitis and choroiditis.
- Optic neuritis.
- Chorioretinitis.
- Anterior segment inflammation.

6. Respiratory diseases:
Symptomatic sarcoidosis.

7. Edematous states:
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.

8. Nervous system:
Acute exacerbations of multiple sclerosis.

Purified Cortrophin Gel is contraindicated for intravenous administration.

Purified Cortrophin 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, hypertension, or sensitivity to proteins derived from porcine sources.

Purified Cortrophin Gel is contraindicated in patients with primary adrenocortical insufficiency or adrenocortical hyperfunction.

Please see the enclosed Purified Cortrophin Gel Prescribing Information (PI) for detailed information including Warnings and Precautions and Adverse Reactions as well as the appropriate use of Purified Cortrophin Gel.

Thank you for your inquiry.

Sincerely,

Steve Wu, PharmD
ANI Pharmaceuticals Medical Information

Use of Purified Cortrophin Gel®(Repository Corticotropin Injection USP) 80 U/mL) in Patients With Uveitis

Abstract

- This document provides summary information pertaining to Purified Cortrophin Gel (repository corticotropin injection USP) and its indication for use in severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as diffuse posterior uveitis
- The active agent in Cortrophin Gel is porcine-derived adrenocorticotropic hormone (ACTH peptide, amino acids 1-39), which is biologically similar to endogenous, human ACTH, and of the same class as other natural-product and synthetic formulations of ACTH.
- To date, there are no published clinical data available that directly interrogate the clinical efficacy and safety of Cortrophin Gel in patients with uveitis.
- Summarized in this document are the results of a literature search of publicly available, peer-reviewed clinical studies of other natural-product and synthetic formulations of ACTH.
    - The included studies are limited to studies in patients with uveitis, in prospective and retrospective studies, case series, or case reports of 1 or more patients. In aggregate, the 5 included studies represent 120 patients with noninfectious uveitis who were administered corticotropin.

Note that this document is for information purposes only. Please refer to the Purified Cortrophin Gel (repository corticotropin injection USP) USPI for full prescribing information. ANI Pharmaceuticals does not recommend the use of its products in any manner inconsistent with the FDA-approved labeling.

To report an adverse event for any ANI Pharmaceuticals product, please call 1-800-308-6755 or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Email: drugsafety@anipharmaceuticals.com.

Introduction

Clinical Background[1]

Purified Cortrophin Gel (repository corticotropin injection USP) is approved by the FDA for use in the treatment of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as allergic conjunctivitis, keratitis, iritis and iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, and chorioretinitis.

Composition of Cortrophin Gel[1]

Purified Cortrophin Gel is a porcine-derived purified corticotropin, adrenocorticotropic hormone (ACTH) in a sterile solution of gelatin. It is made up of a complex mixture of ACTH, ACTH-related peptides and other porcine pituitary-derived peptides.

The drug product is a sterile preparation containing 80 USP units per mL and it contains 0.5% phenol (as preservative), 15.0% gelatin (for prolonged activity), water for injection, and the pH is adjusted with hydrochloric acid and sodium hydroxide.

Purified Cortrophin Gel contains the porcine-derived ACTH (1-39) with the following amino acid sequence:

Purified Cortrophin Gel Clinical Pharmacology

ACTH, the active agent in Purified Cortrophin Gel, is the anterior pituitary hormone which stimulates the functioning adrenal cortex to produce and secrete adrenocortical hormones.[1]

Following administration of a single intramuscular injection of 80 units of Purified Cortrophin Gel to healthy volunteers (n=20) in an open label pharmacodynamic study, the median time (range) to reach peak cortisol concentration was 8 (3 to 12) hours. The baseline corrected geometric mean maximum (CV%) cortisol levels were 34.52 µg/dL (28.2%).[1]

The porcine-derived ACTH (1-39) found in Purified Cortrophin Gel is biologically similar to endogenous human ACTH,[2] and of the same class as synthetic and FDA-approved natural-product formulations of ACTH.[3,4]

ANI conducted a study on the pharmacodynamic effect of Purified Cortrophin Gel, including E_{max}, $AUEC_{0-24}$, and TE_{max}, and compared it with the response of the same or similar depot structures from published literature.[5]

Select Clinical Data in Support of Cortrophin Gel in Uveitis

Study Selection

ANI Pharmaceuticals is not aware of any published (or unpublished) randomized clinical trials or adequately designed studies using Cortrophin Gel for the treatment of noninfectious uveitis that directly interrogate its clinical efficacy and safety.

Below is an overview of peer-reviewed publications of clinical studies that use Acthar Gel, which shares the same porcine-derived active agent, ACTH, as Cortrophin Gel; and synthetic ACTH, which is a truncated ACTH derivative comprising amino acids 1 through 24 of ACTH (1-39). The summary below provides an overview of the available clinical evidence of in-class ACTH-based therapies, with references to source material.

Based on the results of a PubMed search conducted from January 2020 to April 2024, the selection was limited to studies involving ≥10 patients with uveitis. Case reports/studies, and series were excluded from the search. Based on these criteria, one study was identified, representing a total of 91 patients with uveitis.

Study Results Summary

The summary presented here is for the retrospective study by Nelson et al, which reported findings from a US-based, retrospective medical-record evaluation study investigating the use of Acthar Gel in patients with moderate to severe uveitis. Specifically, the study aimed to evaluate patient characteristics, usage patterns of Acthar Gel and concomitant therapies, and physicians' assessments of Acthar Gel treatment effects on patients' health status.[6]

Acthar Gel usage patterns were assessed over a 12-month period, with a total of 21 ophthalmologists participating in the study. The dosing regimen for administration of Acthar Gel varied among the patients included in the study studies, between 40 U-80 U at a frequency of 1-2 times per week. Further details on study treatment and duration are shown in Table 1.[6]

Data Collection

Data were collected from patient medical records, including demographic information, comorbidities, noninfectious uveitis characteristics, treatments for noninfectious uveitis, and physicians' impressions of therapeutic response based on responses to the following questions*: "What is the patient's current status?"* and *"Please select the outcomes that have improved as a result of RCI treatment."*[6]

Outcome Measures

Clinical response to Acthar Gel was evaluated through physicians' assessments of patient status and the type of clinical improvement based on the questions noted in the previous section, and concomitant medication use. Additionally, dosing reductions of concomitant medications were assessed.[6]

Patient Demographics

Among the patients with uveitis who received Acthar Gel within the last 12 months from the start of the study (N=91), most patients had received an average of 2.5 prior therapies, with 50/91 patients (70%) having received prior prednisone at a dose of ≥10 mg/day for ≥6 months. The majority of patients had moderate to severe visual impairment in one or both eyes, and the most commonly reported symptoms were blurred vision (n=81, 89%), light sensitivity (n=41, 45%), floaters (n=40, 44%), and visual loss/acuity (n=40, 44%).[6]

Efficacy Summary

Treatment with Acthar Gel resulted in improved patient status (based on the response to the question "What is the patient's current status?") in 76 patients (84%). Improvements in vision, eye pain, and vitreous haze were observed in 78 (86%), 25 (27%), and 24 (26%) patients, respectively. The number of patients taking concomitant medication decreased both during (n=52, 57%) and after (n=20, 22%) treatment with Acthar Gel. Safety outcomes were not reported in the study.[6]

Treatment Duration

Patients with uveitis included in the study had mean treatment duration between 7.6 –16.7 weeks. Further details on treatment duration are listed in Table 1.[6]

Table 1: Summary of Select Clinical Data on Use of ACTH in Patients with Uveitis

Study	Study Type	RCI, n	Comparator, n	Patient diagnosis	Prior therapies	Study Treatment and duration	Efficacy	Safety
Repository Corticotropin Injection (Brand Name: Acthar Gel)								
Nelson 2019[6]	Retrospective	91	NA	Uveitis anterior uveitis (n = 38, 42%); intermediate uveitis (n = 19, 21%); posterior uveitis (n = 19, 21%); diffuse uveitis/panuveitis (n = 15, 16%)	Before initiation of RCI, all patients were receiving medications for uveitis, with a mean of 2.5 medications (IQR, 2-3)	**RCI regimen:** 40 to 80 IU SC once or twice weekly **Treatment duration:** Mean treatment duration of patients treated at initial dose: 16.7 weeks Mean treatment duration of treatment of patients with tapered dose: 7.6 weeks **Concomitant medications:** Steroid and nonsteroidal anti-inflammatory eye drops, oral steroid, intraocular steroid injections, and biologics	78 patients (86%) had improved vision as a result of RCI treatment, followed by improved pain in 25 patients (27%), and improved vitreous haze in 24 patients (26%). 52 patients (57%) reduced use of concomitant during RCI treatment; this was reduced further to 20 patients (22%) after RCI therapy.	NA (AEs were not recorded)

AE, adverse event; IQR, interquartile range; IU, international unit; NA, not applicable; RCI, repository corticotropin injection.

MED-US-CG-2200029 05/2024.

Citations

1. Purified Cortrophin Gel (Repository Corticotropin Injection USP). Published online 2023. Accessed February 9, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/008975s012lbl.pdf

2. Upton GV, Hollingsworth DR, Lande S, Lerner AB, Amatruda TT. Comparison of purified human and porcine ACTH in man. *J Clin Endocrinol Metab*. 1970;30(2):190-195. doi:10.1210/jcem-30-2-190

3. *Acthar Gel (Repository Corticotropin Injection), for Intramuscular or Subcutaneous Use. Prescribing Information*. Mallinkrodt ARD LLC; 2021. Accessed November 12, 2023. https://acthar.com/Static/pdf/Acthar-PI.pdf

4. *Synacthen Depot Ampoules 1 Mg/Ml. Summary of Product Characteristics (SmPC)*. Atnahs Pharma UK Ltd; 2021. Accessed November 12, 2023. https://www.medicines.org.uk/emc/product/10823/smpc/

5. ANI Pharmaceuticals, Inc. Clinical monograph. Data on file.

6. Nelson WW, Lima AF, Kranyak J, et al. 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. doi:10.1089/jop.2018.0090