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.

This communication may contain confidential, proprietary, and/or privileged information. It is intended solely for the use of the addressee. If you are not the intended recipient, you are strictly prohibited from disclosing, copying, distributing or using any of this information. If you received this communication in error, please contact the sender immediately and destroy the material in its entirety, whether electronic or hard copy.

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 Keratitis

Abstract

- This document provides summary information pertaining to Purified Cortrophin Gel (Repository Corticotropin Injection USP) and its use in severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as keratitis.[1]
- The active agent in Purified 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 FDA-approved natural-product and synthetic ACTH formulations.
- To date, there are no published clinical data available that directly interrogate the clinical efficacy and safety of Purified Cortrophin Gel in patients with keratitis.
- 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 selection of studies is limited to one phase IV, multicenter, open-label study that included a total of 35 patients with keratitis.

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.

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Introduction

Clinical Background

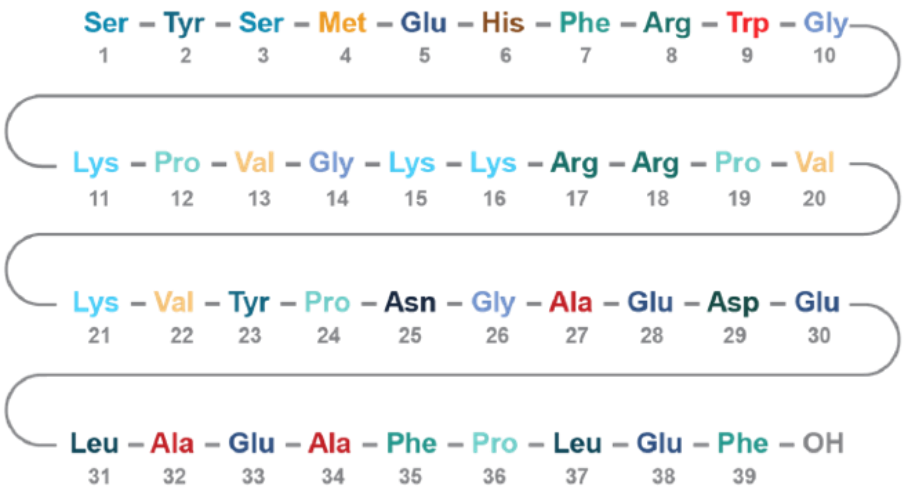
Purified Cortrophin Gel (Repository Corticotropin Injection USP) is approved by the FDA for use in ophthalmic disorders for severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as allergic conjunctivitis, keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.[1]

Composition of Purified Cortrophin Gel

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.[1]

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.[1]

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



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]

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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 other, FDA-approved natural-product and synthetic ACTH formulations.[3–5]

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.[6]

Select Clinical Data in Support of ACTH in Keratitis

Study Selection

ANI Pharmaceuticals is not aware of any published (or unpublished) randomized clinical trials or adequately designed studies using Purified Cortrophin Gel for the treatment of chronic allergic and inflammatory processes involving the eye and its adnexa such as allergic conjunctivitis, keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation, that directly interrogate its clinical efficacy and safety.[1]

The summary below provides an overview of the available clinical evidence of in-class ACTH-based therapies (including Acthar Gel, which shares the same porcine-derived active agent, ACTH, as Purified Cortrophin Gel) with references to source material.

A PubMed search for clinical evidence was performed in February 2024, and restricted results to studies performed in humans, including the phrases “keratitis” and “Cortrophin Gel” or “ACTH” or “repository corticotropin injection” or “synthetic ACTH”. Based on these search parameters, results were limited to one phase 4, multicenter, open-label study in patients with keratitis, representing a total of 35 patients with keratitis to align with the indication as labeled.[7]

Selected Study Results Summary

This summary includes one phase 4, multicenter, open-label study totaling 35 patients with refractory, severe, noninfectious keratitis who received 80 units of Acthar Gel (repository corticotropin injection) subcutaneously twice weekly for 12 weeks, followed by a 4-week taper.[7]

Safety endpoints included the incidence and severity of ocular treatment-emergent adverse events (TEAE), new or worsening cataracts, and mean change from baseline to week 12 in intraocular pressure.[7]

Outcome Measures

The primary outcome measure for this study was improvement in the Impact of Dry Eye on Everyday Life (IDEEL) Questionnaire at week 12. The questionnaire consists of six domains and each domain scores patients’ self-reported experiences on a scale from 0-100. Higher scores indicate better quality of life or treatment satisfaction in that domain, except in *symptom bother*, where higher scores correspond to more bothersome symptoms.[7]

The primary endpoint was the proportion of patients with a ≥12 point improvement (minimal clinically important difference threshold) in the *symptom bother* domain of the IDEEL Questionnaire at week 12

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and the proportion of patients with at least 20%, 30%, and 50% improvement in the *symptom bother* domain of the IDEEL Questionnaire at week 12.[7]

Other outcome measures included mean change from baseline to week 12 in each domain of the IDEEL Questionnaire, each item of the Ocular Discomfort and 4-Symptom Questionnaire, each item of the Visual Analog Scale (VAS), corneal and conjunctival sums of the Corneal and Conjunctival Staining Scale, the Conjunctival Redness Scale, Schirmer's Test, visual acuity, and slit lamp examination.

Twelve weeks of treatment with Acthar Gel resulted in 50% of patients experiencing clinically important improvements in the *symptom bother* domain of the IDEEL Questionnaire. In addition, patients treated with Acthar Gel showed improvements in all other domains of the IDEEL and the Ocular Discomfort and 4-Symptom Questionnaire at week 12.[7]

Patient Demographics

Overall, 35 patients were included in the study, with a mean (SD) age of 63.3 (10.2) years. All patients had severe keratitis in both eyes that had failed treatment with topical immunosuppressants. The mean (SD) and median duration of keratitis were 4.4 (5.4) and 2.6 years, respectively. Scores across the differing symptom scales and questionnaires varied at baseline. Patients reported a mean (SD) score of 65.4 (15.5) on the *symptom bother* domain of the IDEEL Questionnaire and ranked dryness as the worst symptom on the Ocular Discomfort and 4-Symptom Questionnaire.[7]

Efficacy and Safety Profile Summary

By week 12, 17 (50.0%; 95% CI [33.2% to 66.8%]) patients had a ≥12-point improvement in the *symptom bother* domain score of the IDEEL Questionnaire.[7] At week 12, 17 (50.0%; 95% CI [33.2% to 66.8%]), 15 (44.1%; 95% CI [27.4% to 60.8%]), and 5 (14.7%; 95% CI [2.8% to 26.5%]) patients had a ≥20%, ≥30%, and ≥50% improvement in the *symptom bother* domain score of the IDEEL Questionnaire, respectively. These improvements were observed at week 2 and sustained through week 12.[7]

Additional improvements were observed in the following domains at week 2: *impact on daily activities, emotional impact, treatment-related bother,* and *symptom bother*. These were sustained through week 12. Improvements from baseline for the *impact on work* domain were also observed at week 2, though this domain score slightly decreased by week 4 before increasing again at week 6.[7]

Improvements from baseline were observed for each item of the Ocular Discomfort and 4-Symptom Questionnaire after initiation of repository corticotropin injection (RCI) treatment at week 12 and at multiple time points prior. Most patients, 22 (62.9%; 95% CI [46.8% to 78.9%]), reported complete resolution of stinging while only 3 patients (8.6%; 95% CI [0% to 17.8%]) reported complete resolution of dryness.[7]

Moreover, each item of the VAS saw improvements from baseline, notably for *eye dryness* at week 12 (mean [SD]: -22.2 [25.6]; 95% CI [-32.6 to -11.8]) and *eye discomfort* at weeks 2 (mean [SD]: -23.1 [27.5]; 95% CI [-34.7 to -11.5]) and 12 (mean [SD]: -23.9 [25.4]; 95% CI [-34.2 to -13.7]).[7]

Enhancements in the corneal sum as measured by fluorescein staining, conjunctival sum through lissamine green staining, and Schirmer's test results were noted as soon as 4 weeks following the start of RCI therapy and continued up to week 12.[7]

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Generally, Acthar Gel appeared to be well tolerated in this study.[7] One patient experienced a serious TEAE of intentional overdose that was determined to be unrelated to Acthar Gel administration. Notable adverse events included:

- Hypertension (n=2)
- Abdominal pain (n=1)
- Ankle fracture (n=1)
- Blurred vision (n=1)
- Double vision (n=1)
- Fever (n=1)
- Increased viscosity of upper respiratory secretions (n=1)
- Irritability (n=1)
- Polymyalgia rheumatica (n=1)
- Weight gain (n=1)
- Wrist fracture (n=1)
- Upper respiratory tract infection (n=1)

Treatment Duration and Patient Follow-Up

The included study of patients with keratitis had a treatment duration of 12 weeks followed by a 4-week tapering period. Follow-up times were not reported.[7]

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Table 1: Summary of Select Clinical Data in Support of Purified Cortrophin Gel Use in Patients With Keratitis[7]

Study	Study Type	Acthar Gel, N	Patient Population	Study Treatment	Efficacy	Safety
Repository Corticotropin Injection						
Wirta 2021[7]	Phase IV, multicenter, open-label study	35	Patients ≥18 years with persistent severe keratitis despite treatment with topical immunosuppressants	80 U of RCI SQ twice weekly for 12 weeks, followed by a 4-week taper	17 patients had a ≥12-point improvement in the *symptom bother* domain score of the IDEEL Questionnaire 17, 15, and 5 patients had a ≥20%, ≥30%, and ≥50% improvement, respectively, in the *symptom bother* domain score of the IDEEL Questionnaire	12 patients experienced ≥1 TEAE 1 patient (2.8%) had a TEAE (intentional overdose) resulting in death unrelated to the study drug 1 patient each (2.8%) experienced blurred and double vision

IDEEL, Impact of Dry Eye on Everyday Life; RCI, repository corticotropin injection; SQ, subcutaneously; TEAE, treatment-emergent adverse event; U, unit.

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Citations

1. ANI Pharmaceuticals. *Purified Cortrophin™ Gel (Repository Corticotropin Injection USP)*. ANI Pharmaceuticals, Inc.; 11/21. https://cortrophin.com/pdfs/purified-cortrophin-gel-prescribing-information.pdf

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