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) 80U/mL in Patients With Symptomatic Sarcoidosis

Abstract

- This document provides summary information pertaining to Purified Cortrophin Gel (repository corticotropin injection USP) and its indication in respiratory diseases, such as symptomatic sarcoidosis.
- 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 symptomatic sarcoidosis.
- 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 is limited to key studies in patients with sarcoidosis, in prospective and retrospective studies of 6 or more patients. In aggregate, the 4 included studies represent 425 patients with sarcoidosis.

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

Purified Cortrophin® Gel (repository corticotropin injection USP) is approved by the FDA for use in respiratory diseases, such as symptomatic sarcoidosis.[1]

Composition of 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 plasma 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 other, FDA-approved, natural-product and synthetic ACTH formulations.[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 ACTH in Patients With Sarcoidosis

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 respiratory diseases, such as symptomatic sarcoidosis, that directly interrogate its clinical efficacy and safety.

Below is a selection of peer-reviewed publications of clinical studies that use Acthar Gel, which shares the same porcine-derived active agent, ACTH, as Purified 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 results of a PubMed search (performed September 2023), the selection is limited to retrospective or prospective studies including 6 or more patients with sarcoidosis, to align with the indication as labeled. Selection was further limited to publications from January 2011 to December 2023.

Selected Study Results Summary

This summary includes 4 studies (Tables 1 and 2) totaling 425 patients with sarcoidosis who received Acthar Gel.[6-9]

Changes in sarcoidosis symptoms were evaluated across 1 prospective (representing 16 total patients) and 3 retrospective (representing 409 total patients) studies investigating the efficacy of ACTH-based therapy to treat patients with sarcoidosis.[6-9]

While the specific dosing regimens varied among the included studies, in general, Acthar Gel was administered at 40 to 80 U at a frequency of once or twice a week.[6-9]

Outcome Measures

Clinical responses were assessed with a variety of measures, including corticosteroid reduction, diffusion of lung carbon monoxide (DLCO), and standardized uptake value (SUV).[6] One study utilized physicians' assessment of patient status, while another study evaluated patients receiving 1 or more third-line treatments for sarcoidosis.[7,8] The remaining study evaluated the utility and safety of repository corticotropin gel in ocular sarcoidosis.[9]

Patient Demographics

Of the 425 patients with sarcoidosis included in the 4 selected studies who received Acthar Gel, prior treatments for sarcoidosis were reported in 22 patients in 2 studies. In aggregate for disease management, patients received prior steroid therapy or immunomodulatory therapy (see Table 2 for individual study details).[6-9]

Efficacy and Safety Profile Summary

For patients with corticosteroid reduction, there was a reduction in prednisone dosage observed at 7 and 24 weeks (*P*=0.0156 and *P*=0.0078, respectively). Additionally, for lung function, there was a rise in the DLCO observed after 24 weeks of therapy, with no difference between the two ACTH dosage levels (*P*=0.0419). There was also a significant fall in the standardized uptake value (SUV) of the highest lung lesion from a median of 4.0 to 2.9 (*P*=0.0085).[6] In treatments with ACTH, physicians' assessment of patients' current status was improved in 288 (95%), with improvements in overall symptoms (73%), lung function (38%), inflammation (33%), corticosteroid use (32%), quality of life (32%), and fatigue (29%).[7] For patients with sarcoidosis receiving 1 or more third-line therapies, treatment discontinuation was higher for infliximab (55%), adalimumab (58%), or repository corticotropin injection (RCI) (43%) than for rituximab (29%, *P*=0.0075). Compared with ACTH, hazard ratio (HR) for discontinuing therapy due to infection was increased for infliximab (HR=12.14, *P*=0.0134) and adalimumab (HR=9.71, *P*=0.0356). Additionally, compared with ACTH, HR was higher for drug discontinuation due to allergic reactions to infliximab (HR=9.40, *P*=0.0017) or adalimumab (HR=5.83, *P*=0.0273). For patients receiving therapy for ≥2 years, drug survival was significantly shorter for infliximab compared with other therapies (*P*=0.0201).[8] Patients receiving ACTH for ocular inflammation failed to be adequately controlled.[9] Further details are available in Table 1.

Generally, Acthar Gel or synthetic ACTH derivative had the following adverse events (AEs) that included the following (further details per study are in Table 1)[6–9]:

- Jitteriness (n=6)[6]
- Headache (n=3)[6]
- Edema (n=2)[6]
- Nausea (n=1)[6]
- Hyperpigmentation (n=3)[9]
- Elevated blood pressure (n=3)[9]
- Alopecia (n=1)[9]

Treatment Duration and Patient Follow-up

Included studies in patients with sarcoidosis had a treatment duration ranging from 4 months to 24 months, and had follow-up times ranging from 24 weeks to 10 years, with 1 study not reporting.[6–9]

Table 1: Summary of Select Clinical Data in Support of Cortrophin Gel Use in Patients With Sarcoidosis

Study	Study Type	ACTH, n	Comparator, n	Patient Population	Study Treatment	Efficacy	Safety
Repository Corticotropin Injection							
Baughman 2017[6]	Prospective	16	N/A	Chronic pulmonary sarcoidosis	Loading dose of 80 IU SC QD for 10 days, then 4 days off Randomized 1:1 to 40 or 80 IU 2×/week for 22 weeks	Compared to the initial dosage of prednisone, a significant fall in the prednisone dosage at 7 weeks (*P*=0.0156) and 24 weeks (*P*=0.0078) was observed. A significant rise in the DLCO (*P*=0.0419) after 24 weeks of therapy, with no difference between ACTH doses. There was a significant fall in the SUV of the highest lung lesion from median 4.0 to 2.9 (*P*=0.0085).	No significant difference in toxicity between doses, including changes in moodiness, appetite, or bruising. Over the 24 weeks of the study, no significant changes in weight. AEs in 8 patients of jitteriness (n=6), headache (n=3), edema (n=2), and nausea (n=1).
Chopra2019[7]	Retrospective	302	N/A	Sarcoidosis that had previously received ACTH ≤36 months or ongoing ACTH ≥6 months at time of data collection	49 different initial dosing regimens for ACTH: 41 to 80 IU/week (n=122), >80 U/week (n=133), and ≤40 U/week (n=67) 113 patients (38%)	Mean duration of ACTH treatment was 32.5 (±35.6) weeks. Following treatment with ACTH, physicians' assessment of patient's current status was improved in 288 (95%), with improvements in overall symptoms (73%), lung function (38%), inflammation (33%), corticosteroid use (32%), quality of life (32%), and fatigue (29%).	Not reported
Lower 2020[8]	Retrospective	101	Infliximab: 258 Adalimumab: 52 Rituximab: 34	Patients with sarcoidosis who received ≥1 third-line therapies (infliximab, adalimumab, rituximab, or ACTH)	Infliximab: 5 mg/kg IV initial dose, 2 weeks later, Q4W for 1 year, with tapering after 1 year Adalimumab: 40 mg SC Q2W, increased to QW if treatment failure Rituximab: 1000 mg IV initial dose, 2 weeks later, then maintenance every 3 to 8 weeks ACTH: 40 to 80 IU SC twice weekly, tapering to 20 to 40 units QW as tolerated	Discontinuation was higher for infliximab (55%), adalimumab (58%), or RCI (43%) than for rituximab (29%, *P*=0.0075). Compared with ACTH, HR for discontinuing therapy due to infection was increased for infliximab (HR=12.14, *P*=0.0134) and adalimumab (HR=9.71, *P*=0.0356). Compared with ACTH, HR was higher for drug discontinuation due to allergic reactions to infliximab (HR=9.40, *P*=0.0017) or adalimumab (HR=5.83, *P*=0.0273). For patients receiving ≥2 years of therapy, drug survival was significantly shorter for infliximab compared with other therapies (*P*=0.0201).	Major indications for drug discontinuation were infection, allergic reactions, other toxicity, insurance, drug ineffectiveness, remission, and two cases lost to follow-up despite apparent effectiveness of treatment (one each infliximab and ACTH).
Oh 2021[9]	Retrospective	6	N/A	Patients with ocular inflammation treated with ACTH (n=3, biopsy supported OcS; n=1, presumed OcS; n=2, OcS suspects)	80 U twice weekly initially with option to decrease to 80 U QW (n=4). 40 IU twice weekly (n=1) 80 IU twice weekly for 2 weeks, followed by QW for 2 weeks and then 40 IU QW (n=1)	ACTH therapy failed to adequately control ocular inflammation. Five of 6 patients continued to receive local and/or systemic corticosteroids while receiving ACTH therapy and were unable to be weaned off, including 3 patients with active systemic disease who required prednisone or prednisone equivalent of >10 mg/day One patient had quiescence of ocular disease while receiving ACTH and was not receiving steroids	ACTH therapy was stopped in 4 patients due to adverse effects, including hyperpigmentation (n=3), elevated blood pressure ≥160 mmHg systolic and ≥90 mmHg diastolic (n=3) and alopecia (n=1)

ACTH, adrenocorticotropic hormone; DLCO, diffusing capacity of the lungs for carbon monoxide; IM, intramuscularly; IV, intravenously; IU, international unit; N/A, not applicable; OcS, ocular sarcoidosis; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; SUV, standardized uptake value.

Table 2: Prior and Concomitant Medications for Sarcoidosis

Study	Prior therapy	Concurrent therapy
Baughman 2017[6]	Hydroxychloroquine (n=7), methotrexate (n=6), infliximab (n=4), azathioprine (n=3), adalimumab (n=3), leflunomide (n=2), and mycophenolate (n=1); prednisone (n=0)	Prednisone (n=16), methotrexate (n=2), and azathioprine, leflunomide, and hydroxychloroquine (n=1 each)
Chopra2019[7]	Not collected	All major medication classes (n=81; 27%): corticosteroids, nonbiologic oral medications (eg, methotrexate), and biologics
Lower 2020[8]	At least 2 prior lines	Prednisone for 60 (59%), methotrexate for 26 (26%), azathioprine for 19 (19%), hydroxychloroquine for 6 (6%), mycophenolate for 6 (6%), and leflunomide for 3 (3%)
Oh 2021[9]	Corticosteroids (n=6), mycophenolate mofetil (n=3), methotrexate (n=3), cyclosporine (n=1), and azathioprine (n=1)	Topical or systemic corticosteroids (n=5) and methotrexate (n=1); 1 patient had no concurrent therapy

Citations

1. ANI Pharmaceuticals, Inc. Purified Cortrophin® Gel [package insert]. Published online 2023.

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3. Berkovich R, Bakshi R, Amezcua L, et al. Adrenocorticotropic hormone versus methylprednisolone added to interferon β in patients with multiple sclerosis experiencing breakthrough disease: a randomized, rater-blinded trial. *Ther Adv Neurol Disord*. 2017;10(1):3-17. doi:10.1177/1756285616670060

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6. Baughman RP, Sweiss N, Keijsers R, et al. Repository corticotropin for chronic pulmonary sarcoidosis. *Lung*. 2017;195(3):313-322. doi:10.1007/s00408-017-9994-4

7. Chopra I, Qin Y, Kranyak J, et al. Repository corticotropin injection in patients with advanced symptomatic sarcoidosis: retrospective analysis of medical records. *Ther Adv Respir Dis*. 2019;13:175346661988812. doi:10.1177/1753466619888127

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9. Oh DJ, Singh A, Kanu LN, Lobo-Chan AM, MacIntosh PW, Bhat P. Outcomes of repository corticotropin gel for ocular sarcoidosis. *Ocul Immunol Inflamm*. Published online April 7, 2021:1-5. doi:10.1080/09273948.2021.1884887