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

Dosing and Administration of Purified Cortrophin® Gel (Repository Corticotropin Injection USP) 80 U/mL in Patients With Dermatomyositis and Polymyositis

Abstract

- This document provides information pertaining to a comparison of pharmacodynamic responses from ANI Purified Cortrophin® Gel with those from published literature.
- 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 natural-product and synthetic formulations of ACTH.
- Additionally, this document summarizes the dosing and administration of corticotropin for the exacerbation of or as maintenance therapy in selected cases of systemic dermatomyositis (polymyositis) in Medicare-recognized compendia.

Note that this document is for information purposes only. Please refer to the 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]

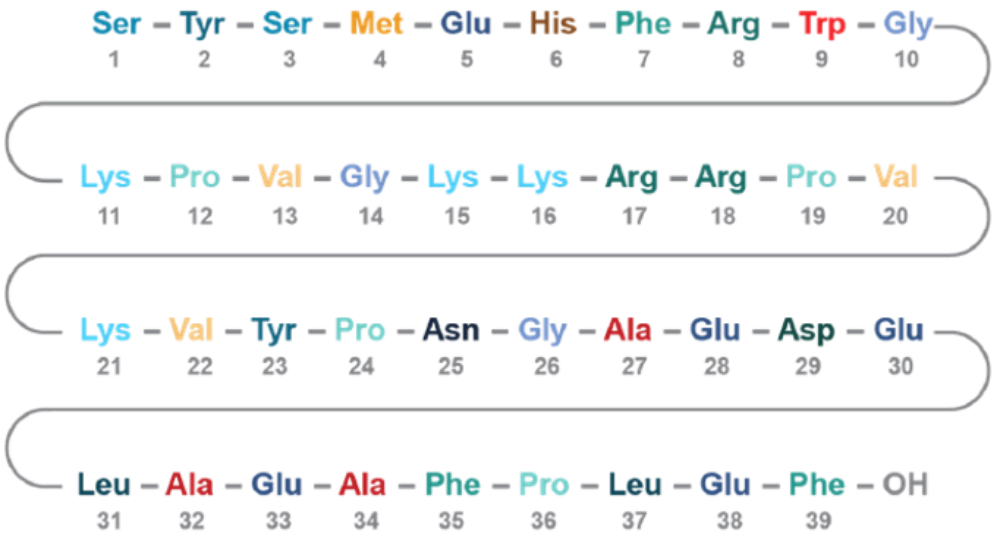
Purified Cortrophin Gel (repository corticotropin injection USP) is approved by the FDA for use in collagen diseases, including systemic dermatomyositis and polymyositis.

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[1]

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.

Following administration of a single intramuscular (IM) 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%).

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]

Comparison of Pharmacodynamic Responses From ANI Purified Cortrophin Gel With Those From Published Literature

Pharmacodynamic activity of Purified Cortrophin Gel was established in healthy volunteers in the open label study described above (see "Purified Cortrophin Gel Clinical Pharmacology").[1]

In brief, prior to administration of Purified Cortrophin Gel, mean baseline plasma cortisol concentrations were consistent with the expected circadian rhythm for cortisol levels under normal physiologic conditions. Following administration of a single IM injection of Purified Cortrophin Gel on Day 1, the baseline-corrected plasma cortisol area under the effect curve over 24 hours ($AUEC_{0-24}$) and the maximum observed effect (E_{max}), were approximately 3.2- and 2.9-fold greater, respectively, compared with baseline cortisol levels.[5]

As a reasonable comparator to Purified Cortrophin Gel pharmacodynamic responses, a literature search was conducted to identify all historical cortisol response studies following administration of depot corticotropin gel products. Ten published studies involving 110 distinct patients were found with relevant data. Purified Cortrophin Gel matched the cortisol responses from the study profiles very well, with estimated weighted geometric mean pharmacodynamic parameters (maximum plasma concentration) and AUEC to the last measurable time point, all within conventional bioequivalence limits (80% to 125%). Time to maximum plasma concentration for Purified Cortrophin Gel was also within the range of values observed in the 10 studies. These observations indicate that the updated Purified Cortrophin Gel elicits cortisol response profiles comparable to those reported in the scientific literature for the same or similar depot corticotropin gel products.[5]

Dosing and Administration of Purified Cortrophin Gel[1]

Standard tests for verification of adrenal responsiveness to corticotropin may utilize as much as 80 units as a single injection or one or more injections of a lesser dosage. Verification tests should be performed prior to treatment with corticotropins. The test should utilize the route(s) of administration proposed for the treatment. Following verification, dosage should be individualized according to the disease under treatment and the general medical condition of the patient. Frequency and dosage of the drug should be determined by considering severity of the disease, plasma and urine corticosteroid levels and the initial response of the patient. Only gradual change in dosing schedules should be attempted, after full drug effects have become apparent.

The chronic administration of more than 40 units daily may be associated with uncontrollable adverse events.

When reduction in dosage is indicated, this should be accomplished gradually by either reducing the amount of each injection or administering injections at longer intervals, or by a combination of both of the above. During reduction of dosage, careful consideration should be given to the disease being treated, the general medical condition of the patient and the duration over which corticotropin was administered.

The product may be administered subcutaneously (SC) or IM.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Compendia Summary: Dosing and Administration of Corticotropin in Dermatomyositis and Polymyositis

Dosing for ACTH for certain indications is listed in Medicare-recognized compendia: American Hospital Formulary Service-Drug Information (AHFS-DI), Truven Health Analytics Micromedex DRUGDEX, Elsevier/Gold Standard Clinical Pharmacology, and Wolters Kluwer Lexi-Drugs. The dosing and administration of corticotropin, summarized below, is supported by each compendium for use during an exacerbation or as maintenance therapy in systemic dermatomyositis and polymyositis.

Please directly reference the compendia for the most up-to-date listing and dosing information.

AHFS-DI[6]	Clinical Pharmacology[7]	DRUGDEX[8]	Lexi-Drugs[9]
40 to 80 U IM/SC every 24 to 72 hours	40 to 80 U IM/SC every 24 to 72 hours	40 to 80 U IM every 24 to 72 hours; Class IIb	40 to 80 U IM/SC every 24 to 72 hours

- AHFS-DI: 40 to 80 units IM or SC every 24 to 72 hours.[6]
- Gold Standard Clinical Pharmacology: 40 to 80 units IM or SC every 24 to 72 hours.[7]
    - Individualize the dose and dosing frequency after considering the disease severity, patient response, and plasma and urine corticosteroid concentrations. After prolonged use, a gradual taper may be necessary in order to avoid adrenal insufficiency or recurrent symptoms.
- Truven Health Analytics Micromedex DRUGDEX: 40 to 80 U IM every 24 to 72 hours.
    - Strength of recommendation for adult dosing: Class IIb – Recommended, in some cases Class IIb recommendation.[8]
    - Individualize dosage based on medical condition of patient with frequency and dose determined by severity of disease and initial response to treatment. Consider tapering dose and increasing injection interval to gradually discontinue and reduce risk of adrenal insufficiency or recurrent symptoms.
- Wolters Kluwer Lexi-Drugs: 40 to 80 units IM or SC every 24 to 72 hours.[9]

- Sudden withdrawal may lead to adrenal insufficiency or recurrent symptoms; tapering the dose and increasing the injection interval prior to discontinuation may be necessary following prolonged administration.

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

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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. AHFS DI (Adult and Pediatric). Corticotropin (pituitary).

7. Clinical Pharmacology (Clinical Key). Corticotropin, ACTH (all populations monograph). https://www.clinicalpharmacology.com/

8. MicroMedex DRUGDEX. Corticotropin. Accessed March 10, 2023. https://www.micromedexsolutions.com/micromedex2/librarian/CS/FBD9AB/ND_PR/evidencexpert/ND_P/evidencexpert

9. Lexicomp. Corticotropin (Lexi-Drugs). Accessed July 24, 2023. https://online.lexi.com/lco/action/home