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 Adults With Systemic Lupus Erythematosus

Introduction

- This document summarizes the dosing and administration of corticotropin for the treatment of systemic lupus erythematosus (SLE), in two Medicare-recognized compendia: Truven Health Analytics Micromedex DRUGDEX and Elsevier/Gold Standard Clinical Pharmacology.
- Additionally, this document provides information pertaining to available evidence supporting the bioequivalence of Cortrophin Gel (Repository Corticotropin Injection USP)[1] and Acthar® Gel.[2] The active agent in Cortrophin Gel is porcine-derived adrenocorticotropic hormone (ACTH peptide, amino acids 1-39),[1] which is biologically similar to endogenous, human ACTH,[3] and of the same class as other, FDA-approved natural-product[2] and synthetic corticotropins.[4]
- This document provides important safety information, including warnings, precautions, and adverse reactions associated with the use of Cortrophin Gel.

Note that this document is for information purposes only. This document may contain information not included in the prescribing information for Cortrophin Gel. The usage of corticotropin being discussed may not have been approved by the FDA as safe and effective. 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.

Background[1]

Purified Cortrophin Gel (Repository Corticotropin Injection USP) is approved by the FDA for the treatment of collagen diseases, such as SLE.[1]

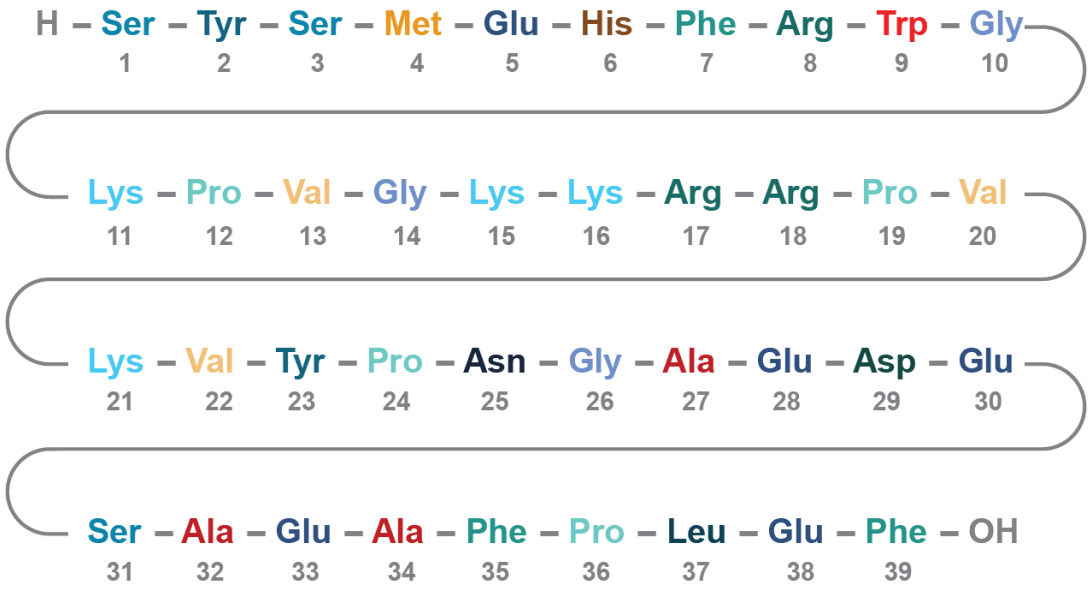
- The active agent in Cortrophin Gel is porcine-derived adrenocorticotropic hormone (ACTH peptide, amino acids 1-39), which is biologically similar to endogenous, human ACTH,[3] and of the same class as other, FDA-approved natural-product and synthetic corticotropins.

Composition of Cortrophin Gel[1]

Cortrophin Gel is a porcine-derived purified corticotropin (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.

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



Cortrophin Gel is the anterior pituitary hormone which stimulates the functioning adrenal cortex to produce and secrete adrenocortical hormones.

To obtain FDA approval, following guidance of the FDA, ANI conducted a study on the pharmacodynamic effect of Cortrophin Gel, including C_{max}, $AUEC_t$, and T_{max}, and compared it with the response of the same or similar depot structures from published literature for bioequivalence.[5]

Pharmacodynamic activity of Cortrophin Gel was established in healthy volunteers in the open-label study described above.[1]

In brief, prior to administration of Cortrophin Gel, mean baseline plasma cortisol concentrations were consistent with the expected circadian rhythm for cortisol levels under normal physiologic conditions.[5]

As a reasonable comparator to 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. Cortrophin Gel estimated weighted geometric mean pharmacodynamic parameters (maximum plasma concentration) and AUEC to the last measurable time point were all within conventional bioequivalence limits (80% to 125%). Time to maximum plasma concentration for Cortrophin Gel was also within the range of values observed in the 10 studies.[5]

Dosing and Administration of 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.

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. 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 intramuscularly (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 SLE

Corticotropin has support for use in collagen diseases, such as SLE, in two Medicare-recognized compendia: Truven Health Analytics Micromedex DRUGDEX and Elsevier/Gold Standard Clinical Pharmacology. The corticotropin dosing supported by each compendium for SLE is summarized below.

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

Indication	Condition	Clinical Pharmacology[6,a]	DRUGDEX[7,b,c]
Collagen diseases	SLE	40 to 80 U IM/SC every 24 to 72 hours	40 to 80 U IM/SC every 24 to 72 hours; Class IIb

IM, intramuscular; SC, subcutaneous; U, unit.

[a]Individualize the dosage 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 to avoid adrenal insufficiency or recurrent symptoms.

[b]Individualize dosage based on medical condition of the patient, with frequency and dosage determined by severity of disease and initial response to treatment. Consider tapering dosage and increasing injection interval to gradually discontinue and reduce risk of adrenal insufficiency or recurrent symptoms.

[c]Strength of recommendation for adult dosing: Class IIa – Recommended, in most cases; Class IIb – Recommended, in some cases.

References

1. Purified Cortrophin™ Gel. Package insert. ANI Pharmaceuticals, Inc. Published online 2021.

2. Acthar® Gel. Package insert. Mallinckrodt ARD LLC. Published online February 2021. Accessed September 16, 2021. https://acthar.com/Static/pdf/Acthar-PI.pdf

3. 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

4. Synacthen® Depot Ampoules 1 mg/ml - Summary of Product Characteristics (SmPC) - (emc). Published October 4, 2021. Accessed October 4, 2021. https://www.medicines.org.uk/emc/product/10823/smpc/

5. ANI Pharmaceuticals, Inc. Data on file.

6. Clinical Pharmacology. Corticotropin, ACTH (all populations monograph). Accessed November 19, 2021. https://www.clinicalpharmacology.com/

7. MicroMedex DRUGDEX. Corticotrophin. Accessed November 19, 2021. https://www.micromedexsolutions.com/home/dispatch/ssl/true