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

Effect of a Single Intramuscular Dose of Purified Cortrophin® Gel (Repository Corticotropin Injection USP) 80 U/mL on Cortisol Levels in Healthy Adult Volunteers

Introduction

- This document summarizes the effect of a single intramuscular dose of Purified Cortrophin Gel on *plasma* cortisol levels in healthy adult volunteers based on the results of a Phase I clinical study.
- The active agent in Cortrophin Gel is porcine-derived adrenocorticotropic hormone (ACTH peptide, amino acids 1-39).[1] Cortrophin Gel is of the same class as other, FDA-approved natural-product (Repository Corticotropin Injection)[2] and synthetic corticotropins[3] and is chemically similar to endogenous, human ACTH.[4]

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 the following disorders:

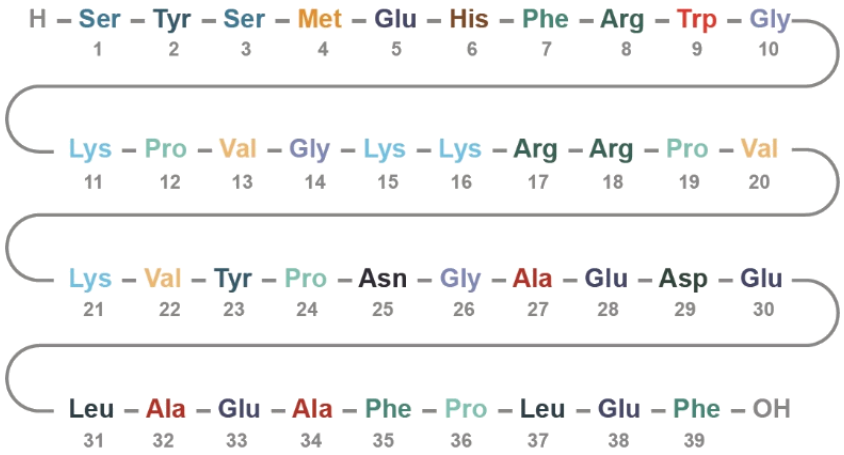
- Rheumatic disorders as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), ankylosing spondylitis, and acute gouty arthritis
- Collagen diseases during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus and systemic dermatomyositis (polymyositis)
- Dermatologic diseases, including severe erythema multiforme (Stevens-Johnson syndrome) and severe psoriasis
- Allergic states, such as atopic dermatitis and serum sickness
- Ophthalmic diseases, including 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, and anterior segment inflammation
- Respiratory diseases, including symptomatic sarcoidosis
- 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
- Nervous system, such as acute exacerbations of multiple sclerosis

Composition of Cortrophin Gel

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.[1]

The drug product is a sterile preparation containing 80 USP corticotropin 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]

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



Cortrophin Gel is the anterior pituitary hormone which stimulates the functioning adrenal cortex to produce and secrete adrenocortical hormones.[1]

The breakdown of ACTH occurs quickly by endogenous enzymes, resulting in a plasma half-life of about 15 minutes.[5]

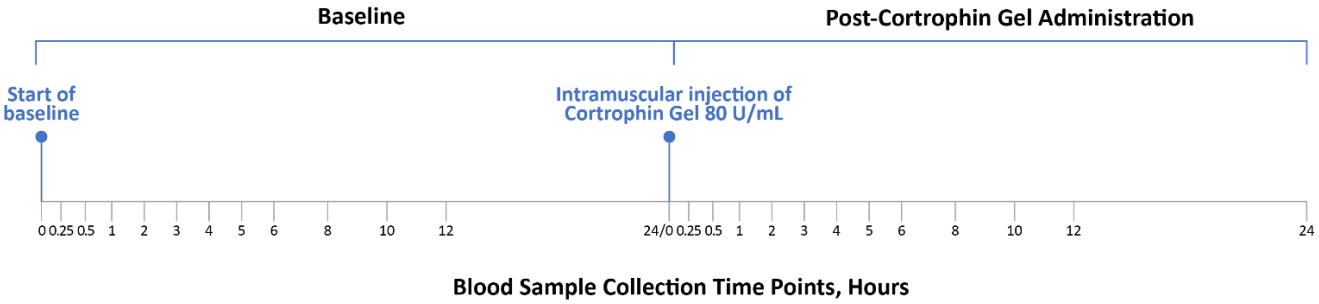
ANI conducted a study, titled CA28049, to assess the pharmacodynamic effect of Cortrophin Gel, including maximum observed effect (E_{max}), area under the effect curve from the time of Cortrophin Gel administration to 24 hours post-administration ($AUEC_{0-24}$), and time to maximum observed effect (TE_{max}) in healthy adult volunteers, the details of which are summarized in the following section.[6,7]

CA28049 Phase I Clinical Study Design[7]

This was a Phase I, open-label, one-time, single-center, pharmacodynamic study. The primary objective was to examine the effect of a single intramuscular dose of Cortrophin Gel on *plasma* cortisol levels in healthy adult volunteers. Pharmacodynamic endpoints included the baseline-corrected $AUEC_{0-24}$ (*plasma* cortisol concentration) and the baseline-corrected E_{max} for cortisol.

The study enrolled 20 healthy adult volunteers who were required to be 18 to 55 years of age at the time of screening for eligibility, which occurred within 28 days prior to the first cortisol sample collection at baseline. *Plasma* cortisol levels were collected at the same time points for 24 hours prior to (ie, at baseline) and following administration of a single intramuscular dose of Cortrophin Gel 80 U/mL (Figure 1). A dosage of 80 U/mL was chosen because it was anticipated to generate a sufficient pharmacodynamic effect for the evaluation of Cortrophin Gel activity. Samples were analyzed for *plasma* cortisol, with a lower limit of quantitation (LLOQ) of 1.24 µg/dL.

Figure 1. *Plasma* Cortisol Blood Sample Collection Time Points



CA28049 Phase I Clinical Study Results[7]

A total of 20 participants enrolled and completed the study (Table 1). Of the 20 participants, 15 were female and 5 were male. The mean age of all participants was 42.6 years ± 8.3 years. Of the participants, 85% were White, 10% Black or African American, and 5% Asian, with 70% Hispanic or Latino and 30% not Hispanic or Latino. All participants were included in the pharmacodynamic analysis and there were no dropouts or missing data in the study.

Table 1. Participant Disposition Summary

Category	Overall
Dosed	20
Completed	20
Discontinued From Study	0

Results show that administration of a single intramuscular injection of Cortrophin Gel 80 U/mL resulted in the expected geometric mean overall ($AUEC_{0-24}$) and peak (E_{max}) exposure of *plasma* cortisol levels for the dosage compared with corresponding baseline values (Figure 2; Table 2). The baseline-corrected median time to reach TE_{max} was 8.0 hours (Table 2).

Figure 2. Baseline-Corrected *Plasma* Cortisol Concentration After a Single Intramuscular Injection of Cortrophin Gel 80 U/mL

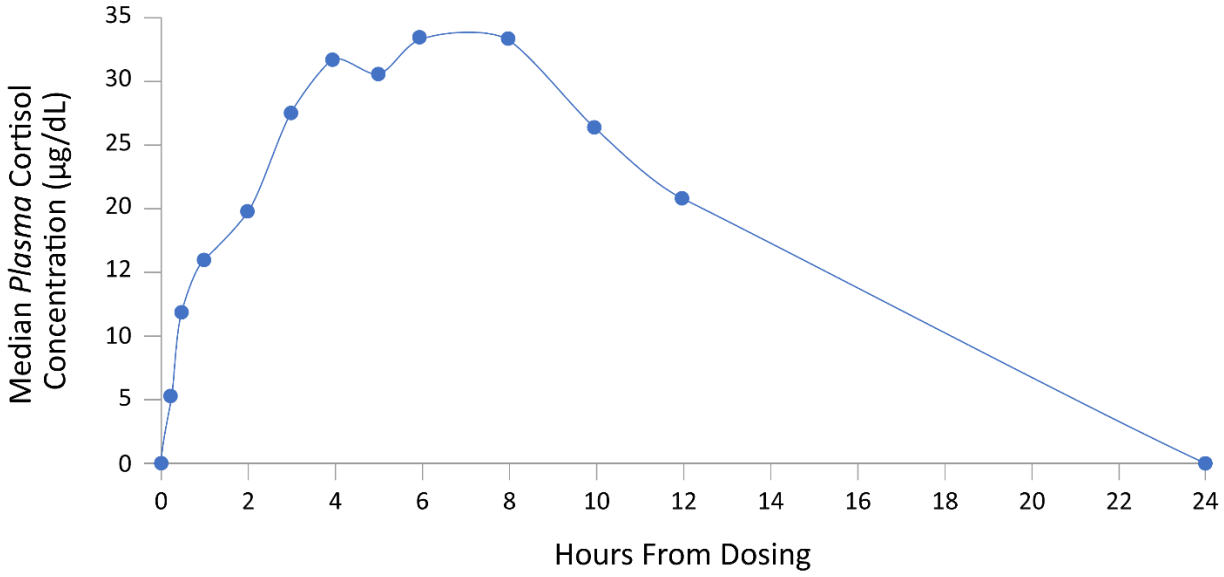


Table 2. Summary of Baseline-Corrected Pharmacodynamic Parameters Following a Single Intramuscular Injection of Cortrophin Gel 80 U/mL

Pharmacodynamic Parameter	Baseline-Corrected Values
$AUEC_{0-24}$ (µg·hr/dL)	434.0 (46.3) [n=20]
E_{max} (µg/dL)	34.52 (28.2) [n=20]
TE_{max} (h)	8.002 (3.00, 12.02) [n=20]
$AUEC_{0-24}$ and E_{max} values are presented as geometric mean (geometric CV%). TE_{max} values are presented as median (min, max).	

Abbreviation: $AUEC_{0-24}$, area under the effect curve from time 0 to 24 hours; CV, coefficient of variation; E_{max}, maximum observed effect; TE_{max}, time to achieve maximum observed effect.

CA28049 Phase I Clinical Study Conclusions

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.[6,7]

Administration of a single intramuscular dose of Cortrophin Gel resulted in increased *plasma* cortisol concentrations compared with baseline concentrations. The overall ($AUEC_{0-24}$) and peak (E_{max}) exposures show Cortrophin Gel stimulates endogenous cortisol production and release.[7]

Comparator Study of Cortrophin Gel With Historic Controls

There were no direct comparative studies between Cortrophin Gel and depot corticotropin gel products. Therefore, any definitive conclusions about this comparison should be avoided. To aid in benchmarking Cortrophin Gel pharmacodynamic responses, a literature search was conducted to identify all relevant 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 appeared to all lie within conventional bioequivalence limits (80% to 125%) among the included study results. Time to maximum *plasma* concentration (TE_{max}) for Cortrophin Gel appeared to be within the range of values observed in the 10 included studies.[6–17]

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