



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

A handwritten signature in black ink that reads "Steve Wu". The signature is written in a cursive, flowing style.

ANI Pharmaceuticals Medical Information

Mechanism of Action of Purified Cortrophin[®] Gel (Repository Corticotropin Injection USP) 80 U/mL in Patients With Systemic Lupus Erythematosus

Abstract

- This document provides summary information pertaining to Purified Cortrophin Gel (Repository Corticotropin Injection USP) and its indication for use during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus (SLE).
- This document summarizes information regarding expression of melanocortin receptors (MCRs) and their potential effects on the adrenal glands and on immune, bone, and cartilage cells.

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 Background¹

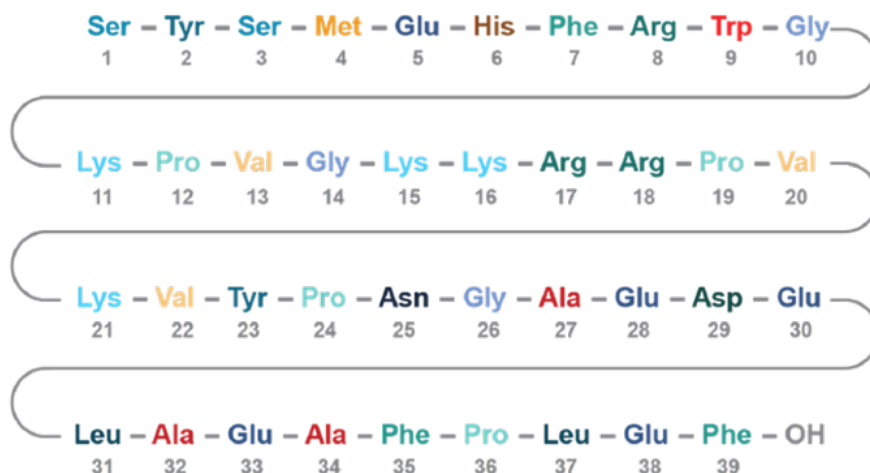
Purified Cortrophin Gel (Repository Corticotropin Injection USP) is approved by the FDA for the treatment of collagen diseases, during an exacerbation or as maintenance therapy in selected cases of SLE and systemic dermatomyositis (polymyositis).

Composition of Purified Cortrophin Gel¹

Purified Cortrophin Gel is a porcine-derived purified corticotropin, adrenocorticotrophic 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), and 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

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 ACTH², and of the same class as other natural-product³ and synthetic ACTH⁴ formulations.

ANI conducted a study on the pharmacodynamic effect of Purified Cortrophin Gel, including maximum observed effect (E_{\max}), area under the effect curve over 24 hours ($AUEC_{0-24}$), and time to achieve maximum observed effect (TE_{\max}), and compared it with the response of the same or similar depot structures from published literature.^{5,6}

Proposed Mechanism of Action of ACTH Potentially Related to SLE

ANI Pharmaceuticals is not aware of any published studies evaluating the mechanism of action of Purified Cortrophin Gel.

The following sections provide a brief overview of select preclinical studies that may help characterize the mechanism of action (MoA) of ACTH and the potential role of melanocortin receptors in mediating some of its therapeutic effects.

Overview of ACTH MOA

While the precise MoA of Purified Cortrophin Gel is not fully understood, its ability to stimulate glucocorticoid production in the adrenal glands has been well characterized. Some preclinical studies suggest that ACTH may have a nonsteroidogenic component to its MoA.

ACTH is a member of the melanocortin family of peptides that are ligands for the MCRs, of which there are 5 known isoforms (MC1R-MC5R).⁷ These endogenous receptors for ACTH are broadly expressed on cells that may play a role in the pathophysiology of SLE.⁸

Use of α -MSH as an Analog of ACTH in Preclinical Studies

Preclinical studies interrogating the function of MCRs often use the melanocortin α -melanocyte stimulating hormone (α -MSH), a modified cleavage product of ACTH. With the exception of MC2R, which is selective for ACTH within the adrenal cortex, α -MSH binds and activates all other MCR family members (MC1R, MC3R, MC4R, and MC5R) analogously to ACTH.^{7,9} In light of limited preclinical evidence in the context of SLE, experiments using α -MSH as well as ACTH are used to highlight the potential nonsteroidogenic action of ACTH on the pathophysiology of SLE.

Preclinical Evidence of Nonsteroidogenic Mechanisms of ACTH

Immune cells that are purportedly driving these abnormal responses, including B cells, T cells, macrophages, and other inflammatory cells, are known to express MCRs, suggesting there is potential for action of ACTH on these various cell types.^{10,11} MCRs are expressed on dendritic cells (DCs) and regulatory T cells (Tregs), which have been implicated in SLE pathophysiology.^{12,13} The following paragraphs describe data suggesting the potential nonsteroidogenic actions of ACTH relating to the pathophysiology of SLE.

MCR Expression on Immune Cells

In isolated peripheral B-cell cultures, ACTH was shown to inhibit B-cell proliferation and immunoglobulin G production without affecting their viability.¹⁴ In another study to evaluate the effects of ACTH on B-

cell gene expression, ACTH treatment resulted in the downregulation of mRNAs critical for B-cell proliferation under activated conditions.¹⁵

In a study of isolated human monocytes, α -MSH inhibited activation of NF- κ B, a transcription factor that regulates immune responses, by various inflammatory stimuli.¹⁶ In another preclinical study using a cell line of human keratinocytes, NF- κ B activation was downregulated by both α -MSH and ACTH (1-39).¹⁷

A preclinical study demonstrated that α -MSH, through binding to MC1R, induced tolerogenic DCs, which increased Tregs both in vitro and in vivo. In vitro, α -MSH-treated Tregs were shown to reduce cutaneous contact allergy. The study also found that α -MSH may induce tolerogenic DCs capable of generating functional Tregs in human blood. These Tregs inhibited the proliferation and cytokine secretion of pathogenic Th17 cells.¹⁸

Melanocortin Expression in Joint Tissue

In patients with different types of arthritis, including those with rheumatic diseases associated with joint inflammation, α -MSH has been found in the synovial fluid of knee joints, suggesting local production of the peptide may occur at sites of inflammation.¹⁹ There is also support for the expression of pro-opiomelanocortin (POMC) and secretion of α -MSH by cultured murine macrophages, with α -MSH increased in the presence of a pro-inflammatory stimulus.²⁰ In another in vitro study using human cultured macrophages, α -MSH inhibited lipopolysaccharide-induced NF- κ B activation.²¹

Citations

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