



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@anipharma.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

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

Abstract

- This document provides summary information pertaining to Purified Cortrophin Gel (repository corticotropin injection USP) and its indication for use in severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as diffuse posterior uveitis.
- This document summarizes select preclinical information regarding expression of melanocortin receptors (MCRs) and the potential effects of Purified Cortrophin Gel, and related class compounds and MCR agonists, on various cell types related to non-infectious uveitis pathology.

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 use in the treatment of ophthalmic diseases for 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

Composition of Purified Cortrophin Gel

Purified Cortrophin Gel is a porcine-derived, purified corticotropin (adrenocorticotrophic hormone [ACTH]), in a sterile solution of gelatin. It comprises 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 Pharmacology¹

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 (AUEC₀₋₂₄), 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 Uveitis

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

Melanocortin Receptors and ACTH

The endogenous receptors of ACTH are the melanocortin receptors, or MCRs, of which there are five known isoforms (MC1R-MC5R). Activation of different isoforms of MCRs may have different downstream effects depending on the tissues or cells on which they are expressed. ACTH binds to all five MCR isoforms.⁷

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.^{8,9} In light of limited preclinical evidence in the context of uveitis, experiments using α -MSH as well as ACTH are used to highlight the potential nonsteroidogenic action of ACTH on the pathophysiology of uveitis.

Steroidogenic Effects of ACTH

ACTH, the active agent in Purified Cortrophin Gel, is known to stimulate production of glucocorticoids such as cortisol in the adrenal glands, a phenomenon which has been well characterized.^{10,11} This effect is attributed to ACTH agonism of MC2R, which is expressed in the adrenal cortex.¹²

MCR Expression on Immune Cells

MCRs are broadly expressed in human tissues, including the adrenal glands, immune cells, and circulating leukocytes.⁷ In human cell-based assays, these include dendritic cells, macrophages, CD4⁺ T_H cells, regulatory T cells (T_{regs}), and B lymphocytes, which suggests a potential target for nonsteroidogenic stimulation by ACTH through these receptors.^{13–18}

Preclinical Studies of Purified Cortrophin Gel in a Mouse Model of Noninfectious Uveitis

In a model of experimental autoimmune uveitis (EAU)-recovered mice, mice were treated with Purified Cortrophin Gel (40 U/kg or 400 U/kg), α -MSH, or placebo (0 U/kg). Post treatment, retinal Ag-specific T cells isolated from spleen of mice treated with 40 U/kg or 400 U/kg Purified Cortrophin Gel demonstrated significantly suppressed expression of proinflammatory cytokines interferon (IFN)- γ ($P \leq 0.001$, both doses) and interleukin (IL)-17 ($P \leq 0.01$, $P \leq 0.001$) compared to placebo. No significant difference in IL-10 was observed between untreated (0 U/kg) and 40 U/kg Purified Cortrophin Gel-treated EAU mice; however, significant ($P \leq 0.05$) suppression in IL-10 was observed in T cells isolated from mice treated with 400 U/kg.¹⁹ These data suggest that Purified Cortrophin Gel suppresses the T-cell response to retinal antigen, but may not activate T_{reg} cell activity. In lipopolysaccharide (LPS)-stimulated peritoneal macrophages from naïve mice, Purified Cortrophin Gel significantly suppressed TNF α , IL-1 β , and IL-10 production. Suppression of TNF- α was dose-dependent, with significant suppression observed starting at 10 U/mL ($P \leq 0.01$) through 80 U/mL ($P \leq 0.0001$). A monophasic suppressive response was observed for IL-1 β at concentrations over 5 U/mL. A similar effect was observed in IL-10 suppression, with a monophasic suppressive response at concentrations greater than 10 U/mL. This suggests that Purified Cortrophin Gel suppresses macrophage activity without induction of suppressor cells or direct macrophage anti-inflammatory activity.¹⁹

The data also suggest that 400 U/kg Purified Cortrophin Gel mediated recovery of EAU, compared to placebo ($P \leq 0.001$), an effect that was similar to α -MSH treatment.¹⁹ This was measured utilizing the previously established EAU score, a clinical and histologic scoring system used to assess the severity of inflammation in the eye. The total score ranges from 0, representing no disease, to 4, representing severe disease. This absolute score encompasses subscores from the optic disc, retinal blood vessels, retinal tissue, and structural damage of each eye.²⁰ In the same model, 400 U/kg Purified Cortrophin Gel appeared to mediate preservation of retinal histology through significant suppression of incidences of retinal folds and vasculitis, similar to α -MSH treatment, compared to placebo ($P < 0.01$).¹⁹

Additional Support for Mechanism of Action by Melanocortin Class Data

Potential Nonsteroidogenic Effects of ACTH on Immune Cells

In cell-based assays, the addition of α -MSH (a melanocortin with shared affinity for MCRs with the exception of MC2R) to LPS- or TNF- α -stimulated monocyte and macrophage cultures was shown to suppress expression of TNF- α , a proinflammatory cytokine, and the activation of NF- κ B, an important proinflammatory mediator.^{15, 21} In another cellular assay, stimulation of tolerogenic dendritic cells with α -MSH induced the expansion of functional T_{regs}.¹⁸ In isolated T cells from C57BL/6 mice, administration

of α -MSH, a melanocortin with shared affinity for MCRs with the exception of MC2R, converted effector T cells into functional T_{reg} cells, thereby mediating TGF- β production.²² In CD28 knockout mice, which are normally deficient in T_{regs}, ACTH promoted more phenotypical T_{reg} cells.¹⁴ ACTH administration has also been shown to reduce immunoglobulin G (IgG) and immunoglobulin M (IgM) secretion and inhibit proliferation of activated B cells in cell cultures.²³

MCR Expression on Ocular Cells and Tissue

In cell-based assays, MC1R expression in human retinal epithelial cells and uveal melanocytes has been reported; MC5R expression has also been shown in retinal epithelial cells in cell cultures.^{24,25} *In vitro* studies from animal models have reported MC1R expression on corneal endothelial cells and MC4R expression on retinal microvessel endothelial cells.^{26,27}

Potential Nonsteroidogenic Effects of ACTH in Ocular Tissue

In cellular models, administration of α -MSH to primary human uveal melanocytes prevented TNF- α stimulated NF- κ B activity vs control, potentially supporting local resistance to inflammatory reactions.²⁸ In another cellular assay, treatment of a human retinal pigment epithelial cell line with α -MSH rescued cells from oxidative stress-induced apoptosis and cell death.²⁴ α -MSH administration also had protective effects against hyperpermeability of retinal endothelial cells vs control in a high glucose-treated retinal microvessel endothelial cell line monolayer transwell culture.²⁷ In a mouse model of corneal injury, local administration of α -MSH post-transcorneal freezing significantly reduced corneal edema and opacity. In the same model, it reduced leukocyte infiltration into the cornea and protected against the apoptosis of corneal endothelial cells while promoting their proliferation.²⁶

Citations

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