

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
ANI Pharmaceuticals Medical Information

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

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 keratitis¹
- This document summarizes information regarding expression of MCRs and the potential effects on immune cells and corneal 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 Background

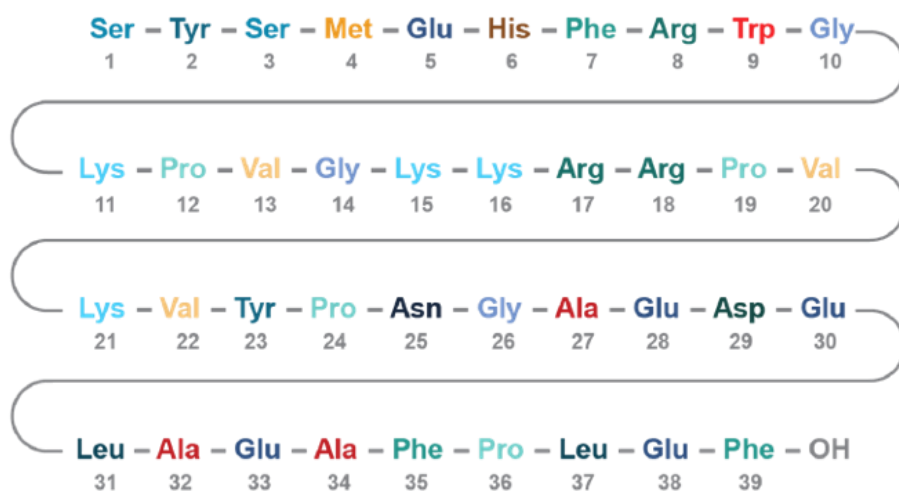
Purified Cortrophin Gel (repository corticotropin injection USP) is approved by the FDA for use in the treatment of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as allergic conjunctivitis, keratitis, iritis and iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, and chorioretinitis.¹

Composition of Cortrophin Gel

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.¹

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.¹

Purified Cortrophin Gel contains the porcine-derived ACTH (1-39) with the following amino acid sequence¹:



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 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 ACTH,² and of the same class as other, FDA-approved natural-product and synthetic ACTH formulations.³⁻⁵

ANI conducted a study on the pharmacodynamic effect of Purified Cortrophin Gel, including E_{max} , AUEC₀₋₂₄, and TE_{max}, and compared it with the response of the same or similar depot structures from published literature.⁶

Proposed Mechanism of Action of ACTH Potentially Related to Keratitis

ANI Pharmaceuticals is not aware of any published (or unpublished) preclinical or clinical trials 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 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 5 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 5 MCR isoforms, while α -MSH is a peptide derivative of ACTH that is often used to elucidate potential nonsteroidogenic actions due to its relatively low affinity for MC2R.⁷

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.^{8,9} This effect is attributed to ACTH agonism of MC2R, which is expressed in the adrenal cortex.¹⁰

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 B lymphocytes, monocytes, macrophages, granulocytes, natural killer cells, CD4⁺ T_H cells, and regulatory T cells (T_{regs}), which suggests a potential target for nonsteroidogenic stimulation by ACTH through these receptors.¹¹⁻¹⁵

Potential Nonsteroidogenic Effects of ACTH on Immune Cells

In cell-based assays, addition of α -MSH to lipopolysaccharide (LPS) or TNF- α -stimulated monocyte and macrophage cultures, suppressed expression of TNF- α , a proinflammatory cytokine, and activation of NF- κ B, an important pro-inflammatory mediator.^{13,16} In another cellular assay, ACTH administration reduced immunoglobulin G and immunoglobulin M accumulation and inhibited proliferation of activated B cells.¹⁷ In CD28 knockout mice, which are normally deficient in T_{regs}, ACTH promoted more phenotypical T_{reg} cells.¹² 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.¹⁸

Citations

1. ANI Pharmaceuticals, Inc. Purified Cortrophin® Gel [package insert]. Published online 2023.
2. Upton GV, Hollingsworth DR, Lande S, Lerner AB, Amatruda TT. Comparison of purified human and porcine ACTH in man. *J Clin Endocrin Metab.* 1970;30(2):190-195. doi:10.1210/jcem-30-2-190
3. Berkovich R, Bakshi R, Amezcua L, et al. Adrenocorticotrophic hormone versus methylprednisolone added to interferon β in patients with multiple sclerosis experiencing breakthrough disease: a randomized, rater-blinded trial. *Ther Adv Neurol Disord.* 2017;10(1):3-17. doi:10.1177/1756285616670060
4. Mallinckrodt ARD LLC. Acthar® Gel [package insert]. Published online February 2021. Accessed November 12, 2023. <https://acthar.com/Static/pdf/Acthar-PI.pdf>
5. Synacthen® Depot Ampoules 1 mg/ml - Summary of Product Characteristics (SmPC) - (emc). Published October 4, 2021. Accessed November 12, 2023. <https://www.medicines.org.uk/emc/product/10823/smpc/>
6. ANI Pharmaceuticals, Inc. Clinical monograph. Data on file.
7. Gong R. Leveraging melanocortin pathways to treat glomerular diseases. *Adv Chronic Kidney Dis.* 2014;21(2):134-151. doi:10.1053/j.ackd.2013.09.004
8. Nussey S, Whitehead S. *Endocrinology: An Integrated Approach*. BIOS Scientific Publishers; 2001. Accessed January 26, 2022. <http://www.ncbi.nlm.nih.gov/books/NBK22/>
9. Jenkins D, Forsham PH, Laidlaw JC, Reddy WJ, Thorn GW. Use of ACTH in the diagnosis of adrenal cortical insufficiency. *Am J Med.* 1955;18(1):3-14. doi:10.1016/0002-9343(55)90200-x
10. Novoselova TV, King PJ, Guasti L, Metherell LA, Clark AJL, Chan LF. ACTH signalling and adrenal development: lessons from mouse models. *Endocr Connect.* 2019;8(7):R122-R130. doi:10.1530/EC-19-0190
11. Andersen GN, Hägglund M, Nagaeva O, et al. Quantitative Measurement of the Levels of Melanocortin Receptor Subtype 1, 2, 3 and 5 and Pro-Opio-Melanocortin Peptide Gene Expression in Subsets of Human Peripheral Blood Leucocytes. *Scand J Immunol.* 2005;61(3):279-284. doi:10.1111/j.1365-3083.2005.01565.x
12. Zhao J, Jiang L, Uehara M, et al. ACTH treatment promotes murine cardiac allograft acceptance. *JCI Insight.* 2021;6(13):e143385. doi:10.1172/jci.insight.143385
13. Yoon SW, Goh SH, Chun JS, et al. α -Melanocyte-stimulating Hormone Inhibits Lipopolysaccharide-induced Tumor Necrosis Factor- α Production in Leukocytes by Modulating Protein Kinase A, p38 Kinase, and Nuclear Factor κ B Signaling Pathways. *J Biol Chem.* 2003;278(35):32914-32920. doi:10.1074/jbc.M302444200
14. Anesi SD, Chang PY, Maleki A, et al. Treatment of Noninfectious Retinal Vasculitis Using Subcutaneous Repository Corticotropin Injection. *J Ophthalmic Vis Res.* 2021;16(2):219-233. doi:10.18502/jovr.v16i2.9086

15. Gong R. The renaissance of corticotropin therapy in proteinuric nephropathies. *Nat Rev Nephrol*. 2011;8(2):122-128. doi:10.1038/nrneph.2011.190
16. Manna SK, Aggarwal BB. α -Melanocyte-stimulating hormone inhibits the nuclear transcription factor NF- κ B activation induced by various inflammatory agents. *J Immun*. 1998;161(6):2873-2880. doi:10.4049/jimmunol.161.6.2873
17. Olsen NJ, Decker DA, Higgins P, et al. Direct effects of HP Acthar Gel[®] on human B lymphocyte activation in vitro. *Arthritis Res Ther*. 2015;17(1):300. doi:10.1186/s13075-015-0823-y
18. Taylor AW, Lee DJ. The Alpha-Melanocyte Stimulating Hormone Induces Conversion of Effector T Cells into Treg Cells. *J Transplant*. 2011;2011:246856. doi:10.1155/2011/246856