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

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

Abstract

- This document provides summary information pertaining to Purified Cortrophin Gel (repository corticotropin injection USP) and its indication to manage symptomatic sarcoidosis.
- It also summarizes information regarding expression of MCRs and the potential effects on immune 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

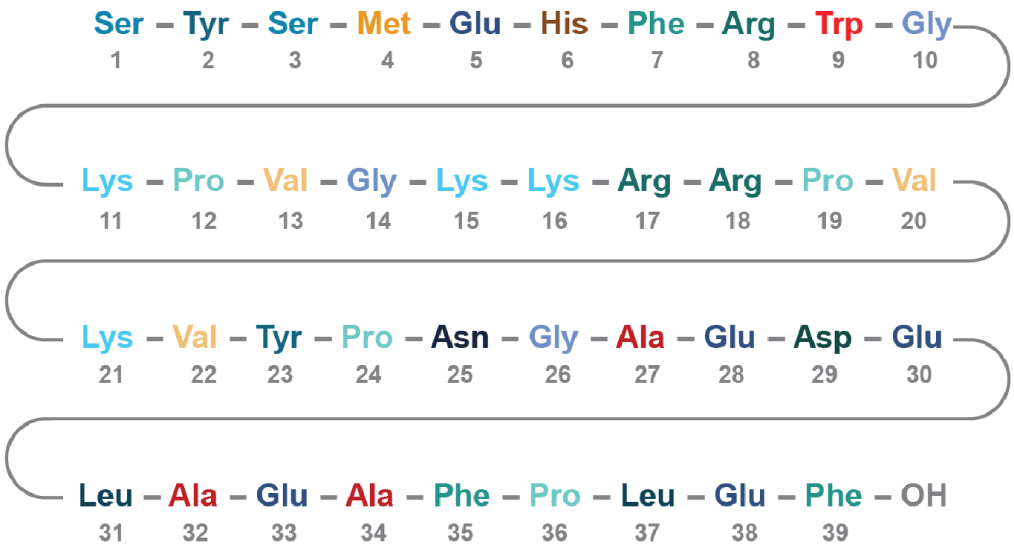
Purified Cortrophin Gel® (repository corticotropin injection USP) is approved by the FDA for use to manage symptomatic sarcoidosis.[1]

Composition of Purified Cortrophin Gel

Purified Cortrophin Gel is a porcine-derived purified corticotropin, adrenocorticotropic hormone (ACTH), in a sterile solution of gelatin. It is made up of a complex mixture of ACTH, ACTH related peptides, and other porcine-derived pituitary 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 sequence[1]:



Purified Cortrophin Gel Clinical Pharmacology

ACTH, the active agent in Purified Cortrophin Gel, is the anterior pituitary hormone that 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 ACTH,[2] and of the same class as other FDA-approved natural-product and synthetic ACTH formulations.[1,3-5]

ANI conducted a study on the pharmacodynamic effect of Purified Cortrophin Gel, including E_{max}, $AUEC_{0-24}$, 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 in Sarcoidosis

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 and corroborative clinical observations 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

ACTH is a member of the melanocortin family of peptides that are ligands for the melanocortin receptors, or MCRs, of which there are 5 known isoforms (MC1R-MC5R).[7] These endogenous receptors for ACTH are broadly expressed on cells important to the pathophysiology of sarcoidosis, and are thought to play an important role in the protective and anti-inflammatory effects of ACTH that are not sufficiently explained by ACTH-stimulated adrenal steroidogenesis.[8]

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.[9,10] This effect is attributed to ACTH agonism of MC2R, which is expressed in the adrenal cortex.[11]

Potential Nonsteroidogenic Effects of ACTH on Inflammatory Cells

Granuloma formation in sarcoidosis is associated with antigen-presenting cells, such as dendritic cells, alveolar macrophages and alveolar epithelial cells, as well as B cells and T cells.[8,12] Each of these cells is known to express one or more MCRs,[13-15] suggesting there is potential for direct, local action of ACTH on various cell types purportedly involved in the pathogenesis of sarcoidosis.[8,16] Pretreatment of monocytes or macrophages with the MCR agonist α-MSH reduced NF-kB response to inflammatory agents.[13,17] Melanocortin receptor activation appears important for T helper cell function, and the melanocortin system may be involved in converting effector T cells into regulatory T cells. [14,15]

Potential Nonsteroidogenic Effects of ACTH in Preclinical Sarcoidosis Models

Preclinical studies of inflammation in acute lung injury that may resemble the pathophysiology of sarcoidosis show a significant reduction of proinflammatory factor release by alveolar macrophages or other immune cells, as well as reduced migration of inflammatory cells in both an MC1R- or an MC3R-dependent manner following treatment with either the corticotropin analog α-MSH or other melanocortins,[12-15] which suggests ACTH may be able to modify the immune response in sarcoidosis.

In a cellular model of sarcoidosis, treating cultured peripheral blood mononuclear cells, which had been isolated from treatment-naïve patients with sarcoidosis, with mycobacterial fragments led to granuloma-like organelle formation within 72 hours, as well as a pronounced proinflammatory cytokine release profile. Treatment with either α-MSH or ACTH shifted the cytokines toward an anti-inflammatory profile in an MC1R-dependent fashion.[22,23]

The results of preclinical studies of lung injury, where fibrosis can occur, suggest that melanocortin treatments can reduce the likelihood of fibrosis progression by inhibiting release of profibrotic mediators, such as transforming growth factor beta, from inflammatory cells including alveolar macrophages.[18,19]

Citations

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