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) 80 U/mL in Patients With Multiple Sclerosis

Abstract

- This document provides summary information pertaining to Purified Cortrophin Gel (repository corticotropin injection USP) and its indication to manage acute exacerbations of multiple sclerosis.
- It also summarizes information regarding expression of MCRs and their potential effects on immune cells, the blood-brain barrier (BBB), and the central nervous system (CNS).

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

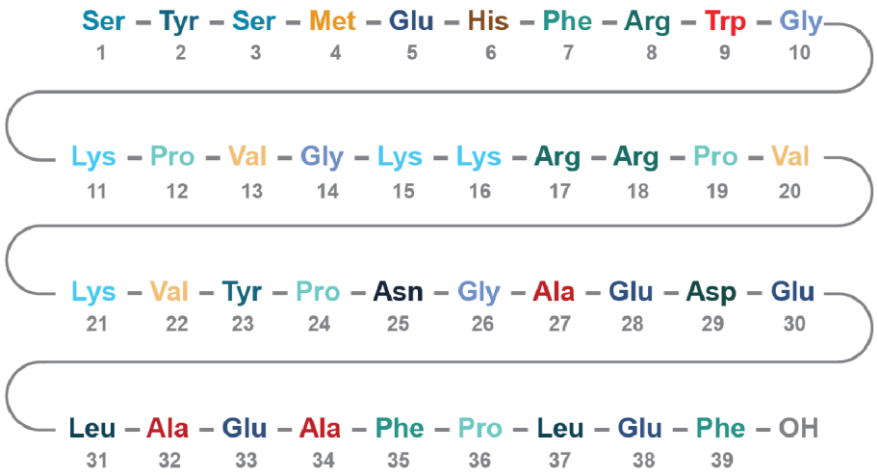
Purified Cortrophin Gel® (repository corticotropin injection USP) is approved by the FDA for use to manage acute exacerbations of multiple sclerosis (MS).[1]

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}, $AUEC_{0\text{-}24}$, 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 Acute Exacerbations in Multiple Sclerosis

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

The endogenous receptors of ACTH are the melanocortin receptors, or MCRs, of which there are 5 known isoforms (MC1R-MC5R). MCRs are broadly expressed in human tissues, including the adrenal glands, immune cells, and within glomerular substructures.[7,8] 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.[9]

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 expressed on a number of circulating leukocytes. 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.[13]

Potential Nonsteroidogenic Effects of ACTH on Inflammatory 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-κB, an important pro-inflammatory mediator.[14,15] In another cellular assay, ACTH administration reduced immunoglobulin G and immunoglobulin M accumulation and inhibited proliferation of activated B cells.[16] In CD28 knockout mice, which are normally deficient in T_{regs}, ACTH promoted more phenotypical T_{reg} cells.[17]

MCR Expression on Endothelial Cells in the Blood-Brain Barrier

In an animal study, MC1R gene expression was reported in isolated rat brain microvessels and cultured brain endothelial cells, suggesting MC1R activation may have direct action on modulating the blood-brain barrier (BBB) in a nonsteroidogenic manner.[18]

Potential Nonsteroidal Effects of ACTH in the BBB

In an in vitro model of the BBB, administration of α-MSH attenuated TNF-α, and IL-1β induced cell permeability of brain endothelial cells and restored morphological changes in cellular junctions of the BBB.[18] Anti-inflammatory effects, including reduction in reactive oxygen species and NF-κB activation, were also observed.[18]

MCR Expression in the Central Nervous System

In vitro studies identified MCR gene expression on astrocytes (MC4R), microglia (MC1R, MC3R, MC4R, and MC5R), and oligodendrocytes (MC1R, MC3R, MC4R, and MC5R), suggesting MCRs may impact the

inflammatory environment in the central nervous system (CNS) via a steroid-independent mechanism.[19–21]

Potential Nonsteroidal Effects of ACTH in the CNS

In a study using primary rat microglia and astrocytes, activation of MC4R by NDP-MSH, an α-MSH analog, demonstrated the release of anti-inflammatory cytokines IL-10 and TGF-β, respectively.[19] Another study using a mouse model of relapsing MS, relapsing/remitting experimental autoimmune encephalomyelitis, showed that the induction of T_{regs} by SVα-MSH, another α-MSH analog, may lead to a reduction in clinical severity of experimental autoimmune encephalomyelitis. This evidence suggests T_{regs} may play an active role in MCR-activated anti-inflammatory events in the CNS.[22]

Administration of ACTH to rat brain cultures containing oligodendrocytes demonstrated its protective effects in vitro against a variety of excitotoxic and inflammation-related cell death mechanisms.[23] ACTH was also found to increase the proliferation and accelerate the differentiation of oligodendrocyte precursors to mature oligodendrocytes.[24]

Citations

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