

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](mailto: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

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# Potential Mechanism of Action of Purified Cortrophin<sup>®</sup> Gel (Repository Corticotropin Injection USP) 80 U/mL in Patients With Acute Exacerbations of Multiple Sclerosis

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## 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.
- This document summarizes information regarding the expression and potential activation of melanocortin receptors (MCRs) through adrenocorticotrophic hormone (ACTH) (and/or its derivatives/analogs) on the adrenal glands, as well as on immune cells, the blood-brain barrier (BBB), and the central nervous system (CNS).

**Note that this document is for informational 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](http://www.fda.gov/medwatch).**

**Email: [drugsafety@anipharmaceuticals.com](mailto:drugsafety@anipharmaceuticals.com)**

## Introduction

### Clinical Background<sup>1</sup>

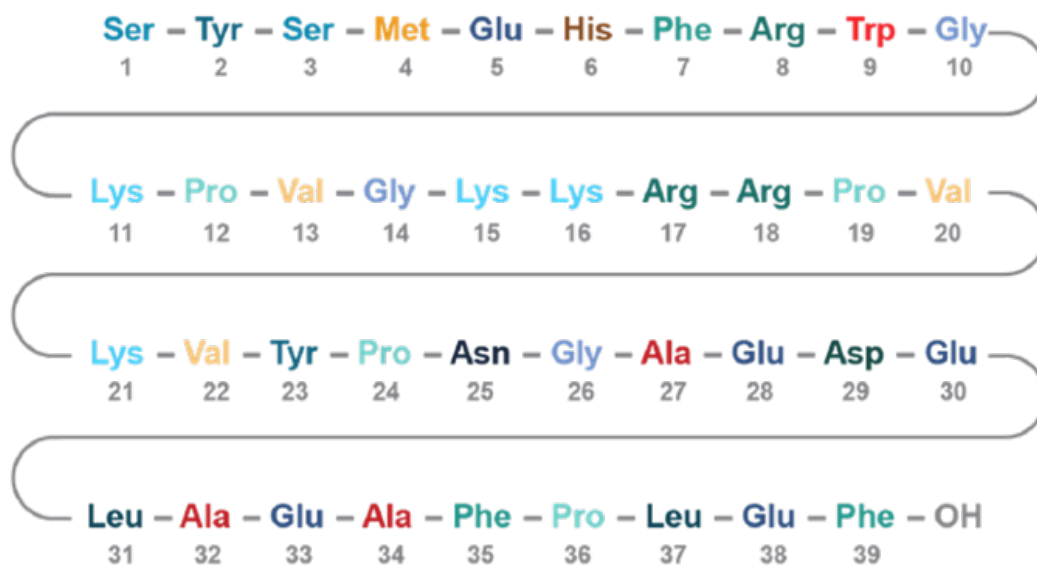
Purified Cortrophin Gel (repository corticotropin injection USP) is approved by the Food and Drug Administration (FDA) to manage acute exacerbations of multiple sclerosis (MS).

### Composition of Cortrophin Gel<sup>1</sup>

Purified Cortrophin Gel is a porcine-derived purified corticotropin (ACTH) in a sterile solution of gelatin. It is comprised 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 that stimulates the functioning adrenal cortex to produce and secrete adrenocortical hormones.<sup>1</sup>

Following administration of a single intramuscular (IM) 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 (coefficient of variation [CV%]) cortisol levels were 34.52 µg/dL (28.2%).<sup>1</sup>

The porcine-derived ACTH (1-39) found in Purified Cortrophin Gel is biologically similar to endogenous human ACTH<sup>2</sup> and of the same class as other natural-product<sup>3</sup> and synthetic ACTH<sup>4</sup> 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<sub>0-24</sub>), and time to achieve maximum observed effect (TE<sub>max</sub>), and compared it with the response of the same or similar depot structures from published literature.<sup>5,6</sup>

## Proposed Mechanism of Action of ACTH Potentially Related to Acute Exacerbations in Multiple Sclerosis

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

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 MCRs in mediating some of its therapeutic effects.

### MCRs and $\alpha$ -MSH

Preclinical studies interrogating the function of MCRs often use the melanocortin alpha melanocyte stimulating hormone ( $\alpha$ -MSH), a modified cleavage product of ACTH. With the exception of MC2R, which is selective for ACTH within the adrenal cortex,  $\alpha$ -MSH binds and activates all other MCR family members (MC1R, MC3R, MC4R, and MC5R) analogously to ACTH.<sup>7,8</sup>

### Steroidogenic Effects of ACTH

ACTH, the active agent in Purified Cortrophin Gel, is known to stimulate the production of glucocorticoids such as cortisol in the adrenal glands, a phenomenon that has been well characterized.<sup>9,10</sup> This effect is attributed to ACTH agonism of MC2R, which is expressed in the adrenal cortex.<sup>11</sup>

### MCR Expression on Immune Cells

Studies of human peripheral blood showed that MCRs were expressed on a variety of circulating leukocytes, including B lymphocytes, monocytes, macrophages, granulocytes, natural killer cells, CD4<sup>+</sup> T<sub>h</sub> cells, and regulatory T cells (T<sub>regs</sub>).<sup>12</sup> This expression pattern suggests that these cells could serve as potential targets for nonsteroidogenic stimulation by ACTH, suggesting the potential for ACTH to exert direct, local action on various cell types that may be involved in the pathogenesis of MS.<sup>12</sup>

### Potential Nonsteroidogenic Effects of ACTH on Immune Cells

In cell-based assays, the addition of  $\alpha$ -MSH to lipopolysaccharide (LPS)- or tumor necrosis factor (TNF)- $\alpha$ -stimulated monocyte and macrophage cultures suppressed the expression of TNF- $\alpha$ , a proinflammatory cytokine, and activation of nuclear factor-kappa B (NF- $\kappa$ B), an important proinflammatory mediator.<sup>13,14</sup> In another cellular assay, ACTH administration reduced immunoglobulin G and immunoglobulin M

accumulation and inhibited proliferation of activated B cells.<sup>15</sup> In cluster of differentiation 28 (CD28) knockout mice, which are normally deficient in T<sub>regs</sub>, ACTH promoted more phenotypical T<sub>reg</sub> cells.<sup>16</sup>

### MCR Expression on Endothelial Cells in the BBB

In an animal study, MC1R gene expression was reported in isolated rat brain microvessels and cultured brain endothelial cells, which suggests there is potential for the action of ACTH on these various cell types in a nonsteroidogenic manner.<sup>17</sup>

### Potential Nonsteroidal Effects of ACTH in the BBB

In an *in vitro* model of the BBB, the administration of  $\alpha$ -MSH reduced the permeability induced by TNF- $\alpha$  and interleukin (IL)-1 $\beta$  in brain endothelial cells and helped restore morphological changes in cellular junctions of the BBB.<sup>17</sup> A reduction in reactive oxygen species and NF- $\kappa$ B activation was also observed, indicating the potential modulation of cellular responses within the BBB.<sup>17</sup>

### MCR Expression in the CNS

*In vitro* studies have demonstrated the expression of MCR genes in various CNS cell types: MC4R on astrocytes and MC1R, MC3R, MC4R, and MC5R on both microglia and oligodendrocytes. This expression pattern suggests that MCRs may influence the activities of these glial cells, potentially affecting processes such as cellular signaling and interactions within the CNS through mechanisms that do not involve endogenous steroids.<sup>18–20</sup>

### Potential Nonsteroidal Effects of ACTH in the CNS

In an *in vitro* study using primary rat microglia and astrocytes, the activation of MC4R by [Nle(4), D-Phe(7)]-MSH (NDP-MSH) (an  $\alpha$ -MSH analog) demonstrated the release of anti-inflammatory cytokines IL-10 and transforming growth factor (TGF)- $\beta$ , respectively.<sup>18</sup> Another study using a mouse model of relapsing MS (relapsing/remitting experimental autoimmune encephalomyelitis) demonstrated that the induction of T<sub>regs</sub> by SV $\alpha$ -MSH (an  $\alpha$ -MSH analog) was associated with the modulation of immune cell activities, including a potential reduction in the activation of autoreactive CD4(+) T cells.<sup>21</sup>

The administration of ACTH to rat brain cultures was shown to reduce oligodendrocyte death induced by agents such as staurosporine, glutamate, hydrogen peroxide, and slow nitric oxide release.<sup>22</sup> ACTH was also found to increase the proliferation and accelerate the differentiation of oligodendrocyte precursors to mature oligodendrocytes.<sup>23</sup>

## Citations

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