

Potential Mechanism of Action of Purified Cortrophin[®] Gel (Repository Corticotropin Injection USP) 80 U/mL in Patients With Proteinuria Due to Nephrotic Syndrome

Abstract

- This document provides summary information pertaining to Purified Cortrophin Gel (repository corticotropin injection USP) and its indication to induce a diuresis or a remission of proteinuria in nephrotic syndrome (NS) without uremia of the idiopathic type of that due to lupus erythematosus.
- It also summarizes information regarding expression of MCRs on and the potential effects on immune cells and kidney cells.

In response to an unsolicited request, the slides “ACTH in Nephrotic Syndrome: Proposed Mechanism of Action” MED-US-CG-2300022 must be provided in conjunction with this letter.

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.

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Introduction

Clinical Background

Purified Cortrophin Gel™ (repository corticotropin injection USP) is approved by the FDA for use to induce a diuresis or a remission of proteinuria in nephrotic syndrome (NS) without uremia of the idiopathic type or that due to lupus erythematosus.¹

Composition of Purified 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 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 Potentially Related to Proteinuria Due to Nephrotic Syndrome

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- κ B, an important pro-inflammatory mediator.^{14,15} In another cellular assay, ACTH administration reduced IgG and IgM accumulation and inhibited proliferation of activated B cells.¹⁶ In CD28 knockout mice, which are normally deficient in T_{regs}, ACTH promoted more phenotypic T_{reg} cells.¹⁷

MCR Expression on Kidney Cells

Human and animal tissue expression studies point to several MCR isoforms variously being expressed in kidney parenchyma, including podocytes, mesangial cells, tubular epithelial cells, and glomerular endothelial cells.⁷ Additionally, compared to healthy donors, the damaged glomeruli of patients with membranous nephropathy and focal segmental glomerulosclerosis have significantly elevated MC1R expression.¹⁸

Potential Nonsteroidogenic Effects of ACTH in the Kidney

In a mouse model of THSD7A-associated membranous nephropathy, ACTH administration was reported to statistically significantly reduce proteinuria (estimated by urinary albumin to creatinine ratios) in a dose-dependent manner on Days 2 and 3 post-ACTH treatment ($P < 0.05$ vs vehicle on Days 2 and 3); reductions appeared to plateau above ACTH treatment with 60 IU/kg body weight. ACTH administration was also found to statistically significantly protect against glomerular injury (assessed by preserved fluorescence immunohistochemistry staining of podocin) ($P < 0.05$ vs vehicle).¹⁹

In rodent models of nephrotic injury similar to that seen in NS, stimulation of MC1R-expressing podocytes through α -MSH (a nonspecific melanocortin peptide that has no appreciable affinity for MC2R) was reported to reduce proteinuria, improve glomerular morphology, and reduce oxidative stress.⁹ Other preclinical data suggest that agonism of MC1R on podocytes elicits its effects through stabilization of cytoskeletal components important to the integrity of foot processes and maintenance of the glomerular filtration barrier.^{18,20}

MCR Expression on Liver Cells

MCR gene expression has been reported in human liver tissue, most notably MC1R, suggesting activation of MCRs may have direct action on liver cells that is not dependent upon the steroidogenic pathway.²¹

Potential Nonsteroidal Effects of ACTH in Dyslipidemia

In liver cell cultures, treatment with ACTH promotes uptake of low-density lipoprotein (LDL).²² Activation of MC1R by α -MSH and LD211 (a specific MC1R agonist) receptors on human hepatocytes *in vitro* has been reported to reduce cellular cholesterol content and enhance LDL and high-density lipoprotein (HDL) uptake.²³

ACTH has been shown to have a lipid-lowering effect in healthy volunteers,²⁴ and ACTH treatment was associated with improvement in serum lipoprotein pattern and glomerular function in patients with NS.²⁵ In patients with idiopathic membranous nephropathy, the results of a prospective trial suggested that lipid-lowering drugs may be effective in controlling proteinuria.²⁶

Citations

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