Mallinckrodt Announces Publication of Two Journal Manuscripts with Clinical and Economic Evidence for Acthar® Gel (Repository Corticotropin Injection)

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– Clinical findings from historical manuscript published in *Clinical Drug Investigation* reinforce the efficacy, safety profile, and use of Acthar Gel in appropriate patients across 12 autoimmune and inflammatory indications1 –

– Economic findings from manuscript published in *ClinicoEconomics and Outcomes Research* support Acthar Gel's clinical and economic benefits for patients across nine autoimmune and inflammatory indications2 –

DUBLIN, Oct. 10, 2023 /PRNewswire/ -- Mallinckrodt plc (OTCMKTS: MNKTQ), a global specialty pharmaceutical company, today announced the publication of two journal manuscripts reinforcing the clinical and economic evidence supporting the efficacy, safety profile, continued use, and cost-effectiveness of Acthar Gel for appropriate patients across a range of FDA-approved autoimmune and inflammatory disease indications.1,2

Mallinckrodt's clinical manuscript titled "Acthar Gel Treatment for Patients with Autoimmune and Inflammatory Diseases: A Historical Perspective and Characterization of Clinical Evidence" was published on October 4, 2023 in the journal, *Clinical Drug Investigation.* Mallinckrodt's health economics manuscript titled "Acthar Gel (RCI): A Narrative Literature Review of Clinical and Economic Evidence" was published on June 24, 2023 in *ClinicoEconomics and Outcomes Research.*

Acthar is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides. Acthar Gel is approved by the U.S. Food and Drug Administration (FDA) for the treatment of several autoimmune disorders and medical conditions known to cause inflammation.3

Please see indications and Important Safety Information below.

Authored by Jeffrey Kaplan, M.D., Kansas City Multiple Sclerosis & Headache Center, and colleagues, "Acthar Gel Treatment for Patients with Autoimmune and Inflammatory Diseases: A Historical Perspective and Characterization of Clinical Evidence," sought to review the history of Acthar and the findings of existing literature on preclinical and clinical studies that have investigated the mechanism of action, safety profile, efficacy, and real-world effectiveness of Acthar. The indications addressed in the study include the treatment of inflammatory diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis and polymyositis (DM/PM), multiple sclerosis (MS) relapse, inflammatory ocular diseases, sarcoidosis, and nephrotic syndrome (NS).1

- As a result of this analysis spanning more than 20 preclinical mechanistic studies and 15 clinical studies with a combined enrollment of approximately 900 patients, and the publication of over 500 manuscripts and abstracts to date, the findings reinforce the safety profile, efficacy, and usage of Acthar in appropriate patients with inflammatory diseases for whom standard treatments may have become ineffective or associated with intolerable side effects.1

"Acthar® Gel has an established efficacy and safety profile supported by robust clinical research and experience," said **Dr. Kaplan.** "For patients and providers managing the challenges associated with chronic inflammatory and autoimmune conditions, the findings of this study further elucidate Acthar's proposed mechanism of action and reinforce the extensive history of clinical evidence that has shown its potential to improve health and treatment outcomes across a range of FDA-approved indications."1

This publication is accompanied by an Audiocast.
All six authors across specialties representing key Acthar Gel indications researched in this study discuss a brief overview of the manuscript, including the history of Acthar, its mechanism of action (MOA), and clinical characteristics, in addition to introductions on each author and reflections on their own personal experiences with Acthar in clinical practice.

Authored by George J. Wan, Ph.D., M.P.H., Vice President, Evidence Generation and Data Sciences at Mallinckrodt, and colleagues, "Acthar Gel (RCI): A Narrative Literature Review of Clinical and Economic Evidence" reviewed key studies of clinical efficacy and healthcare resource utilization and cost from 1956 to 2022 to summarize the key clinical and economic findings among nine FDA-approved Acthar Gel indications: infantile spasms (IS), MS relapse, RA, SLE, DM/PM, ocular inflammatory diseases (primary uveitis and severe keratitis), symptomatic sarcoidosis, and proteinuria in NS.2

- This analysis found that among all nine medical conditions studied, Acthar has shown effectiveness in reducing symptoms, improving functioning and well-being, reducing disease relapse, and/or increasing disease remission.2
- Economic data from this analysis suggests that Acthar is a cost-effective, value-based treatment option for MS relapse, RA, and SLE. Other economic benefits have been demonstrated for IS, MS relapses, RA, SLE, and DM/PM, including reduced hospitalizations, length of stay, inpatient and outpatient services, and emergency department visits.2

"The findings of this health-economics analysis deepen our understanding of Acthar's ability to serve as a cost-effective, value-based treatment option across multiple FDA-approved indications studied – including how appropriate use of Acthar may be associated with reduction of healthcare utilization costs such as total hospitalizations, patient length of stay, and concurrent treatment burden, such as the use of corticosteroids,"2 said **Wan.**

Data collected in a retrospective analysis may have errors or omissions. Outcomes may be influenced by therapies not evaluated in the study and the clinical outcomes may not be solely attributable to Acthar.

These studies were funded by Mallinckrodt Pharmaceuticals.

ABOUT DERMATOMYOSITIS/POLYMYOSITIS (DM/PM)
DM/PM are rare inflammatory diseases that cause progressive muscle weakness,4 usually in the muscles closest to the trunk of the body.5 For instance, muscle weakness associated with PM involves those in the hips, thighs, shoulders, upper arms, and neck.6 DM also causes skin rashes.7 People of all ages can be affected, though it usually occurs between the ages of 40-60 and is more common in women.7,8

ABOUT INFANTILE SPASMS (IS)
IS is a rare seizure disorder that affects approximately 2,500 children in the U.S. every year.9 It most commonly occurs between three and seven months of age.9 Sometimes called West syndrome, IS demands early identification, diagnosis, and treatment to help limit lasting effects.9 Children with IS generally have one or more of the following symptoms: a certain type of seizure (called "spasms"), a disorganized and chaotic brain-wave pattern called hypsarrhythmia as recorded on an EEG (electroencephalogram).10

ABOUT MULTIPLE SCLEROSIS (MS)
MS is a chronic neurologic disorder that affects the central nervous system (i.e., the brain and spinal cord).11 Symptoms can include fatigue, mobility issues, numbness or tingling, vision problems, muscle spasticity, tremors, and cognitive changes.12,13 More than eight in 10 people with MS will experience a relapse, or flare-up, that brings new or worsening symptoms.12

ABOUT PROTEINURIA IN NEPHROTIC SYNDROME (NS)
NS is a collection of symptoms that occur when the blood vessels in the kidney begin to leak excess protein in the urine, a condition called proteinuria.14 A variety of diseases and underlying disorders damage the kidneys and cause proteinuria in people with NS.14 These etiologies can include glomerular diseases such as: idiopathic membranous nephropathy, focal segmental glomerulosclerosis, minimal change disease, membranoproliferative glomerulonephritis, lupus nephritis, and IgA nephropathy.15,16,17,18 In these and other related disorders, the glomeruli, or small blood vessels that work as the kidney's filtering system, are damaged.14

Proteinuria is one of the most important adverse prognostic factors for progression to end stage renal failure in patients with glomerular disease. One of the goals of treating NS includes reducing or eliminating proteinuria.19

ABOUT RHEUMATOID ARTHRITIS (RA)
RA is an autoimmune disease.20 It is a chronic condition that causes pain, stiffness, and swelling of the joints – all symptoms caused by inflammation.20 An estimated 1.5 million U.S. adults are living with RA.20

ABOUT SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
SLE is an autoimmune disease in which the immune system produces antibodies to cells within the body leading to possible inflammation and tissue damage.21 It is the most common form of lupus,21 a condition that impacts an estimated 1.5 million Americans.22 Far more of those diagnosed with lupus are women, often between the ages of 15-44.21 Lupus is characterized by periods of illness "flares" and remissions and the disease can affect the joints, skin, brain, lungs, kidneys, and blood vessels.21 Symptoms may include fatigue, pain or swelling in joints, skin rashes, and fevers.21

ABOUT SYMPTOMATIC SARCOIDOSIS
Sarcoidosis is a challenging and rare multisystem disease.23 In some cases, the symptoms may come and go throughout a lifetime.23 This is referred to as symptomatic sarcoidosis.23 In people with sarcoidosis the immune system overreacts, forming clumps of cells called granulomas that result in inflammation to the body's tissues.24 The disease can impact any organ, but it most often impacts the lungs, lymph nodes, eyes, and skin.25 Nearly 90 percent of people with sarcoidosis will suffer lung problems.25 Concomitant involvement of organs outside of the lungs is common, occurring in more than half of all sarcoidosis cases, according to one study.26

ABOUT UVEITIS
Uveitis is a mix of acute or chronic inflammatory eye disorders that affects the uveal tract (a layer of tissue just behind the outer layer of the eye) and adjacent structures, including the sclera, cornea, vitreous humor, retina, and optic nerve head.27,28,29,30 Symptoms vary based on the site of inflammation, but can include decreased vision, eye pain, tearing, redness, light sensitivity, and floaters.27,28 Uveitis has numerous etiologies, associated conditions, and underlying immune responses that complicate its diagnosis and treatment.28,31 Uveitis accounts for up to 10% of cases of legal blindness in the United States. In the United States, the annual incidence (occurrence of new cases) of uveitis ranges between 17.4 and 52.4 per 100,000 person-years.32,33,34 It most affects individuals of working age.28

ABOUT SEVERE KERATITIS
Keratitis is a painful inflammation of the cornea which can result in partial or total loss of vision if left untreated and is a significant cause of ocular morbidity around the world.35 It can result from infectious agents (e.g., microbes including bacteria, fungi, amebae, and viruses) or from non-infectious causes (e.g., eye trauma, chemical exposure, and ultraviolet exposure).36 Conditions that affect the integrity of the ocular surface epithelium (exposure keratitis, neurotrophic keratitis, keratomalacia, recurrent corneal erosions) may also lead to development of sterile corneal ulcers.37 Non-infectious corneal ulcers may be associated with various collagen vascular or other autoimmune diseases, sometimes as the presenting sign of the disease.37

INDICATIONS

Acthar Gel is indicated for:

- Inducing a diuresis or a remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus
- Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age
- Treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown Acthar to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease

- Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation
- Symptomatic sarcoidosis
- Treatment during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus
- Treatment during an exacerbation or as maintenance therapy in selected cases of dermatomyositis (polymyositis)
- 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

IMPORTANT SAFETY INFORMATION

Contraindications

Acthar is contraindicated:

- For intravenous administration
- In infants under 2 years of age who have suspected congenital infections
- With concomitant administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of Acthar
- In patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction, or sensitivity to proteins of porcine origin

Warnings and Precautions

- The adverse effects of Acthar are related primarily to its steroidogenic effects
- Acthar may increase susceptibility to new infection or reactivation of latent infections
- Suppression of the hypothalamic-pituitary-adrenal (HPA) axis may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress (e.g., trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA axis suppression after stopping treatment
- Cushing's syndrome may occur during therapy but generally resolves after therapy is stopped. Monitor patients for signs and symptoms
- Acthar can cause elevation of blood pressure, salt and water retention, and hypokalemia. Monitor blood pressure and sodium and potassium levels
- Acthar often acts by masking symptoms of other diseases/disorders. Monitor patients carefully during and for a period following discontinuation of therapy
- Acthar can cause gastrointestinal (GI) bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain GI disorders. Monitor for signs of perforation and bleeding
- Acthar may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changes, and severe depression to psychosis. Existing conditions may be aggravated
- Patients with comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar in patients with diabetes and myasthenia gravis
- Prolonged use of Acthar may produce cataracts, glaucoma, and secondary ocular infections. Monitor for signs and symptoms
- Acthar is immunogenic and prolonged administration of Acthar may increase the risk of hypersensitivity reactions. Cases of anaphylaxis have been reported in the postmarketing setting. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH and Acthar activity
- There may be an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver
- Long-term use may have negative effects on growth and physical development in children. Monitor pediatric patients
- Decrease in bone density may occur. Bone density should be monitored in patients on long-term therapy

Adverse Reactions

- Commonly reported postmarketing adverse reactions for Acthar include injection site reaction, asthenic conditions (including fatigue, malaise, asthenia, and lethargy), fluid retention (including peripheral swelling), insomnia, headache, and blood glucose increased
- The most common adverse reactions for the treatment of infantile spasms (IS) are increased risk of infections, convulsions, hypertension, irritability, and pyrexia. Some patients with IS progress to other forms of seizures; IS sometimes masks theses seizures, which may become visible once the clinical spasms from IS resolve

Pregnancy

- Acthar may cause fetal harm when administered to a pregnant woman

Please see full Prescribing Information for additional Important Safety Information.

ABOUT MALLINCKRODT
Mallinckrodt is a global business consisting of multiple wholly owned subsidiaries that develop, manufacture, market and distribute specialty pharmaceutical products and therapies. The company's Specialty Brands reportable segment areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, hepatology, nephrology, pulmonology, ophthalmology, and oncology; immunotherapy and neonatal respiratory critical care therapies; analgesics; cultured skin substitutes and gastrointestinal products. Its Specialty Generics reportable segment includes specialty generic drugs and active pharmaceutical ingredients. To learn more about Mallinckrodt, visit www.mallinckrodt.com.

Mallinckrodt uses its website as a channel of distribution of important company information, such as press releases, investor presentations and other financial information. It also uses its website to expedite public access to time-critical information regarding the company in advance of or in lieu of distributing a press release or a filing with the U.S. Securities and Exchange Commission (SEC) disclosing the same information. Therefore, investors should look to the Investor Relations page of the website for important and time-critical information. Visitors to the website can also register to receive automatic e-mail and other notifications alerting them when new information is made available on the Investor Relations page of the website.

CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS
This release contains forward-looking statements, including with regard to Acthar® Gel, its potential to improve health and treatment outcomes, its ability to reduce healthcare utilization costs, and its potential impact on patients. The statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those in the forward-looking statements: satisfaction of regulatory and other requirements; actions of regulatory bodies and other governmental authorities; changes in laws and regulations; issues with product quality, manufacturing or supply, or patient safety issues or adverse side effects or adverse reactions associated with Acthar; pricing pressure on Mallinckrodt's products due to legal changes or changes in insurers' reimbursement practices from recent increased public scrutiny of healthcare and pharmaceutical costs; the reimbursement practices of governmental health administration authorities, private health coverage insurers and other third-party payers; and other risks identified and described in more detail in the "Risk Factors" section of Mallinckrodt's most recent Annual Report on Form 10-K and other filings with the SEC, all of which are available on its website. The forward-looking statements made herein speak only as of the date hereof and Mallinckrodt does not assume any obligation to update or revise any forward-looking statement, whether as a result of new information, future events and developments or otherwise, except as required by law.

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