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Mallinckrodt Announces Publication of New Data on Acthar® Gel (Repository Corticotropin Injection) in Rheumatoid Arthritis, Systemic Lupus Erythematosus and Dermatomyositis/Polymyositis Published in Open Access Rheumatology: Research and Reviews

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-- Retrospective chart review assessing Acthar Gel treatment utilization and patterns in 92 patients suggests improvement in symptoms across three disease states in a real-world setting --

STAINES-UPON-THAMES, United Kingdom, March 4, 2020 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, today announced findings from a retrospective medical record analysis to assess practice patterns and outcomes of Acthar® Gel (repository corticotropin injection) in the treatment of the immune-mediated diseases rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and dermatomyositis/polymyositis (DM/PM). Results of the study were recently published online in *Open Access Rheumatology: Research and Reviews*.

Acthar Gel 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) as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in RA, including juvenile RA (selected cases may require low-dose maintenance therapy), and for use during an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).[1] Please see Important Safety Information for Acthar Gel below.

The study, titled "Treatment with Repository Corticotropin Injection in Patients with Rheumatoid Arthritis, Systemic Lupus Erythematosus, and Dermatomyositis/Polymyositis," examined 92 adult patients (≥18 years of age) – 54 with RA, 30 with SLE and 8 with DM/PM – who were treated at 14 U.S. clinical sites with Acthar Gel between January 1, 2011 and February 15, 2016. Researchers collected data on patient demographics, disease and treatment history; Acthar Gel dosing, frequency and duration; concomitant medication use; and physicians' assessments of outcomes and adverse events. Results of the analysis showed that across all three patient populations, the most frequently reported reasons for initiating treatment with Acthar Gel were inadequate response to prior therapies, acute exacerbation or flare of disease, and need for an alternative therapy. The findings also suggest that patients' symptoms improved with Acthar Gel as reported by physicians' impression of overall change after treatment initiation and over the course of the study. Among 57 patients with data on physician impression of change, 78.1 percent of patients with RA, 94.7 percent of patients with SLE and 66.7 percent of patients with DM/PM had a rating of improved. Further, the mean time to best impression of change was 3.4±2.5 months for RA, 4.3±2.7 for SLE, and 3.4±1.6 for DM/PM.

"All three immune-mediated diseases examined in this study can be difficult to manage, and patients can often experience debilitating disease flares and exacerbations," said **Tunde Otulana, M.D., Senior Vice President and Chief Medical Officer at Mallinckrodt**. "The study suggests that Acthar Gel may have been associated with an improvement in disease exacerbations and symptoms, and it provides insights into real-world practice patterns and outcomes associated with Acthar Gel therapy that may help inform decision-making among clinicians in managing these conditions."

Further, the study builds on the company's Phase 4 study of Acthar Gel in RA patients (open-label portion, n=259; randomized, placebo-controlled, blinded, withdrawal portion, n=154) presented at the European Congress of Rheumatology 2019 (EULAR), June 12-15 in Madrid. The randomized, placebo-controlled, double-blind two-part study demonstrated that significantly more patients with persistently active RA who met response criteria at week 12 (63 percent of patients in the open-label period who achieved low disease activity (LDA) as assessed by Disease Activity Score 28-joint count Erythrocyte Sedimentation Rate (DAS28-ESR) of <3.2 at 12 weeks) maintained LDA with Acthar Gel (62 percent) versus placebo (43 percent, P<0.05) at week 24. In the double-blind period of the study (weeks 12-24), adverse events (AEs) were reported in 33 percent of the Acthar Gel treatment group and 40 percent of the placebo group. In the open-label period of the study (weeks 0-12), AEs were reported in 38 percent of patients. Overall AEs observed in the study were consistent with previous trials of Acthar Gel. The study was subject to study limitations, including that the results may not be solely attributable to Acthar Gel.

Key Findings:[2]

- Data were collected from 92 patients (54 with RA; 30 with SLE; 8 with DM/PM) with mean age of over 49 years who were predominately female. Data collection spanned the 12 months prior to and up to 12 months following initiation of Acthar Gel treatment.
- Prior to treatment with Acthar Gel, most patients had been treated with multiple therapies, including the most common therapies, which were as follows:
    - Patients with RA:
        - 94 percent non-biologic disease-modifying antirheumatic drugs (DMARDs)
        - 87 percent corticosteroids

        - 87 percent biologic DMARDS
    - Patients with SLE:
        - 80 percent corticosteroids
        - 73 percent nonbiologic DMARDs
        - 57 percent immunosuppressive drugs
    - Patients with DM/PM:
        - 88 percent immunosuppressive drugs
        - 75 percent corticosteroids
- In all three populations, the most common starting dose of Acthar Gel was 80 U twice weekly, which was used for 84 percent of RA patients, 75 percent of SLE patients, and 86 percent of DM/PM patients.
- Changes in Acthar Gel dose occurred in 33 percent of patients with RA, 43 percent of patients with SLE, and 25 percent of patients with DM/PM.
- The usual dose of Acthar Gel is 40-80 units given intramuscularly or subcutaneously every 24-72 hours.
- The mean duration of treatment was:
    - 4.8 months in RA
    - 6.5 months in SLE
    - 6.8 months in DM/PM
- Among the 57 patients with data on physicians' impression of change (n=32; 59 percent with RA, n=19; 63 percent with SLE, and n=6; 75 percent with DM/PM), physicians rated their impression of change as improved in 78.1 percent of patients with RA; 94.7 percent of patients with SLE; and 66.7 percent of patients with DM/PM.
- Adverse events were reported in 14 patients (26 percent) with RA; 5 patients with SLE (17 percent); and 2 patients with DM/PM (25 percent). Serious adverse events were reported in 1 patient with RA (2 percent); 4 patients with SLE (13 percent); and 1 patient with DM/PM (12 percent).
- Acthar Gel treatment was discontinued in 24 (44 percent) RA patients, 6 (20 percent) SLE patients, and 5 (63 percent) DM/PM patients. The most common reasons for discontinuation of Acthar Gel were reported as:
    - Patients with RA:
        - AEs related to Acthar Gel (38 percent)
        - Disease resolution/remission/treatment no longer necessary (17 percent)
        - Physician choice (17 percent)
    - Patients with SLE:
        - Treatment-related AEs (50 percent)
    - Patients with DM/PM:
        - AEs related to Acthar Gel (40 percent)
        - Lack of efficacy/inadequate response/disease progression (40 percent)

Study Limitations:[2]

- The study is limited by its retrospective design, small sample size and reliance on medical records, some of which had missing data and may have had errors and omissions (such as care received at other clinics).
- Disease activity is difficult to assess through medical records, as it is not routinely recorded or recorded with the appropriate timing to allow evaluation of clinical response to therapy.
- Utilization of physicians' impression of change as a descriptive endpoint was a subjective measure relying on an individual clinician's own standards of improvement and was not available for 38 percent of the records evaluated.
- The study's retrospective noncomparative design did not allow researchers to determine if patients were responding to other therapies.
- Results are exploratory and should be interpreted with these limitations in mind.
- Results may not be solely attributable to Acthar Gel.

The study was funded by Mallinckrodt.

About Rheumatoid Arthritis
RA is an autoimmune disease. It is a chronic condition that causes pain, stiffness, and swelling of the joints—all symptoms and signs caused by inflammation.[3] An estimated 1.5 million U.S. adults are living with RA.[4] Treatment is aimed at stopping inflammation to put the disease in remission and relieve symptoms.[5] Nonsteroidal anti-inflammatory drugs are used to ease symptoms whereas corticosteroids, disease-modifying anti-rheumatic drugs and biologics are used to slow down the disease activity.[5]

About Systemic Lupus Erythematosus
SLE is an autoimmune disease in which the immune system produces antibodies to cells within the body leading to widespread inflammation and tissue damage.[6] It is the most common form of lupus, a condition that impacts an estimated 1.5 million Americans.[7] Ninety percent of those diagnosed with lupus are women, often between the ages of 15-44.[8] Lupus is characterized by periods of illness "flares" and remissions and the disease can affect the joints, skin, brain, lungs, kidneys, and blood vessels. Symptoms and signs may include fatigue, pain or swelling in joints, skin rashes, and fevers.[6]

About Dermatomyositis/Polymyositis
DM/PM are rare inflammatory diseases that cause progressive muscle weakness.[9] For instance, muscle weakness associated

with PM involves those in the hips, thighs, shoulders, upper arms and neck.[10] DM also causes skin rashes.[9] People of all ages can be affected, though it usually occurs in adults between the ages of 45-60 and is more common in women.[11,[12]]

Acthar Gel (repository corticotropin injection) Indications

Acthar® Gel (repository corticotropin injection) is indicated for:

- Treatment during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus
- Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age
- The treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown Acthar Gel 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
- Inducing a diuresis or a remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus
- Treatment during an exacerbation or as maintenance therapy in selected cases of systemic dermatomyositis (polymyositis)
- The treatment of symptomatic sarcoidosis
- 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
- Treatment of 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

IMPORTANT SAFETY INFORMATION

Contraindications

- Acthar should never be administered intravenously
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar
- Acthar is contraindicated where congenital infections are suspected in infants
- Acthar 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, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins

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-axis (HPA) 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 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. Blood pressure, sodium and potassium levels may need to be monitored
- 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 GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Monitor for signs of bleeding
- Acthar may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changes, and severe depression, and 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. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH activity
- There is 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 for patients on long-term therapy
- Pregnancy Class C: Acthar has been shown to have an embryocidal effect and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Adverse Reactions

- Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in

glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain
- Specific adverse reactions reported in IS clinical trials in infants and children under 2 years of age included: infection, hypertension, irritability, Cushingoid symptoms, constipation, diarrhea, vomiting, pyrexia, weight gain, increased appetite, decreased appetite, nasal congestion, acne, rash, and cardiac hypertrophy. Convulsions were also reported, but these may actually be occurring because some IS patients progress to other forms of seizures and IS sometimes mask other seizures, which become visible once the clinical spasms from IS resolve

Other adverse events reported are included in the full Prescribing Information.

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's areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, nephrology, pulmonology and ophthalmology; immunotherapy and neonatal respiratory critical care therapies; analgesics 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 includes forward-looking statements concerning Acthar Gel including its potential impact on patients and anticipated benefits associated with its use. 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; 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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