Acthar® Gel

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ACTHAR® GEL safely and effectively. See full prescribing information for ACTHAR GEL.

ACTHAR GEL (repository corticotropin injection), for intramuscular or subcutaneous use. Initial U.S. Approval: 1952

---------- RECENT MAJOR CHANGES ----------

- Warnings and Precautions, Immunogenicity Potential (5.10) 10/2021
- Warnings and Precautions, Use in Pregnancy (5.14) - removal 10/2021

---------- INDICATIONS AND USAGE ----------

- Acthar Gel is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age. (1.1)
- Acthar Gel is indicated for the treatment of exacerbations of multiple sclerosis in adults. (1.2)
- Acthar Gel may be used for the following disorders and diseases: rheumatic (1.3); collagen (1.4); dermatologic (1.5); allergic states (1.6); ophthalmic (1.7); respiratory (1.8); and edematous state (1.9).

---------- DOSAGE AND ADMINISTRATION ----------

- In the treatment of infantile spasms, the recommended dose is 150 U/m^2 divided into twice daily intramuscular injections of 75 U/m^2. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period. (2.1)
- In the treatment of acute exacerbations of multiple sclerosis, daily intramuscular or subcutaneous doses of 80-120 units for 2-3 weeks may be administered. It may be necessary to taper the dose. (2.2)
- In the treatment of other disorders and diseases, dosing will need to be individualized depending on the disease under treatment and the medical condition of the patient. It may be necessary to taper the dose. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

- 5 mL multi-dose vial containing 80 USP units per mL. (3)

---------- CONTRAINDICATIONS ----------

Acthar Gel is contraindicated:

- for intravenous administration (4)
- in infants under 2 years of age who have suspected congenital infections (4)
- with concomitant administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of Acthar Gel (4)
- 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 origin (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination or reactivation of latent infections. Signs and symptoms of infection may be masked. (5.1)
- Adrenal Insufficiency after Prolonged Therapy: Monitor for effects of hypothalamic-pituitary-adrenal axis suppression after stopping treatment. (5.2)
- Cushing's Syndrome: May occur after prolonged therapy. Monitor for signs and symptoms. (5.2)
- Elevated Blood Pressure, Salt and Water Retention, and Hypokalemia: Monitor blood pressure and sodium and potassium levels. (5.3)
- Masking of Symptoms of Other Underlying Disease/Disorders: Monitor patients for signs of other underlying disease/disorders that may be masked. (5.5)
- Gastrointestinal Perforation and Bleeding: There is a risk for gastric ulcers and bleeding. There is an increased risk of perforation in patients with certain GI disorders. Signs and symptoms may be masked. Monitor for signs of perforation and bleeding. (5.6)
- Behavioral and Mood Disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression and psychosis. Existing conditions may be aggravated. (5.7)
- Comorbid Diseases: Symptoms of diabetes and myasthenia gravis may be worsened with treatment. (5.8)
- Ophthalmic Effects: Monitor for cataracts, infections and glaucoma. (5.9)
- Immunogenicity Potential: Neutralizing antibodies with chronic administration may lead to a loss of endogenous ACTH activity. (5.10)
- Use in Patients with Hypothyroidism or Liver Cirrhosis: May result in an enhanced effect. (5.11)
- Negative Effects on Growth and Physical Development: Monitor pediatric patients on long term therapy. (5.12)
- Decrease in Bone Density: Monitor for osteoporosis in patients on long term therapy. (5.13)

---------- ADVERSE REACTIONS ----------

- Commonly reported postmarketing adverse reactions for Acthar Gel include injection site reaction, asthenic conditions (including fatigue, malaise, asthenia and lethargy), fluid retention (including peripheral swelling), insomnia, headache, and blood glucose increased. (6.2)
- The most common adverse reactions (5% or greater in the recommended twice daily dosing group) for the treatment of infantile spasms are increased risk of infections, convulsions, hypertension, irritability, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt at 1-800-844-2830 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------

- Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy. (7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pediatric Use: Prolonged use of Acthar Gel in children may inhibit skeletal growth. If use is necessary, it should be given intermittently with careful observation. (5.12, 5.13, and 8.4)
- Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: 10/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Infantile Spasms

Acthar Gel is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.

1.2 Multiple Sclerosis

Acthar Gel is indicated for 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.

1.3 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.

1.4 Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).

1.5 Dermatologic Diseases

Severe erythema multiforme, Stevens-Johnson syndrome.

1.6 Allergic States

Serum sickness.

1.7 Ophthalmic Diseases
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.

1.8 Respiratory Diseases
Symptomatic sarcoidosis.

1.9 Edematous State
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.

2 DOSAGE AND ADMINISTRATION

2.1 Specific Recommended Dosage Regimen for Infantile Spasms in Infants and Children Under 2 Years of Age
In the treatment of infantile spasms, Acthar Gel must be administered intramuscularly. The recommended regimen is a daily dose of 150 U/m^2 (divided into twice daily intramuscular injections of 75 U/m^2) administered over a 2-week period. Dosing with Acthar Gel should then be gradually tapered over a 2-week period to avoid adrenal insufficiency. The following is one suggested tapering schedule: 30 U/m^2 in the morning for 3 days; 15 U/m^2 in the morning for 3 days; 10 U/m^2 in the morning for 3 days; and 10 U/m^2 every other morning for 6-days.

Acthar Gel is typically dosed based on body surface area (BSA). For calculation of body surface area, use the following formula

$$BSA(m^2) = \sqrt{\frac{weight\,(\mathrm{kg}) \times height\,(\mathrm{cm})}{3600}}$$

2.2 Recommended Dosage Regimen for the Treatment of Acute Exacerbations in Adults with Multiple Sclerosis
The recommended dose is daily intramuscular or subcutaneous doses of 80-120 units for 2-3 weeks for acute exacerbations.

Dosage should be individualized according to the medical condition of each patient. Frequency and dose of the drug should be determined by considering the severity of the disease and the initial response of the patient.

Although drug dependence does not occur, sudden withdrawal of Acthar Gel after prolonged use may lead to adrenal insufficiency or recurrent symptoms which make it difficult to stop the treatment. It may be necessary to taper the dose and increase the injection interval to gradually discontinue the medication.

2.3 Recommended Dosage Regimen for Other Indications for Adults and Children Over 2 Years of Age
Dosage should be individualized according to the disease under treatment and the general medical condition of each patient. Frequency and dose of the drug should be determined by considering severity of the disease and the initial response of the patient.

The usual dose of Acthar Gel is 40-80 units given intramuscularly or subcutaneously every 24-72 hours.

Although drug dependence does not occur, sudden withdrawal of Acthar Gel after prolonged use may lead to adrenal insufficiency or recurrent symptoms which make it difficult to stop the treatment. It may be necessary to taper the dose and increase the injection interval to gradually discontinue the medication.

2.4 Preparation
Acthar Gel should be warmed to room temperature before using.

Caution should be taken not to over-pressurize the vial prior to withdrawing the product.

3 DOSAGE FORMS AND STRENGTHS
5 mL multi-dose vial containing 80 USP Units per mL.

4 CONTRAINDICATIONS
Acthar Gel 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 Gel.
- 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 origin.

5 WARNINGS AND PRECAUTIONS
The adverse effects of Acthar Gel are related primarily to its steroidogenic effects. Not all of the adverse events described below have been seen after treatment with Acthar Gel, but they might be expected to occur because they are steroidogenic effects *[see Adverse Reactions (6.3)]*.

5.1 Infections
Acthar Gel may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic infections. Patients with latent tuberculosis or tuberculin reactivity should be observed closely, and if therapy is prolonged, chemoprophylaxis should be instituted.

5.2 Cushing's Syndrome and Adrenal Insufficiency Upon Withdrawal
Treatment with Acthar Gel can cause hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing's syndrome. These conditions should be monitored especially with chronic use.

Suppression of the HPA may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Patients should be monitored for signs of insufficiency such as weakness, hyperpigmentation, weight loss, hypotension and abdominal pain.

The symptoms of adrenal insufficiency in infants treated for infantile spasms can be difficult to identify. The symptoms are non-specific and may include anorexia, fatigue, lethargy, weakness, excessive weight loss, hypotension and abdominal pain. It is critical that parents and caregivers be made aware of the possibility of adrenal insufficiency when discontinuing Acthar Gel and should be instructed to observe for, and be able to recognize, these symptoms *[see Patient Counseling Information (17)]*.

The recovery of the adrenal gland may take from days to months so patients should be protected from the stress (e.g., trauma or surgery) by the use of corticosteroids during the period of stress.

The adrenal insufficiency may be minimized in adults and infants by tapering of the dose when discontinuing treatment.

Signs or symptoms of Cushing's syndrome may occur during therapy but generally resolve after therapy is stopped. Patients should be monitored for these signs and symptoms such as deposition of adipose tissue in characteristics sites (e.g., moon face, truncal obesity), cutaneous striae, easy bruisability, decreased bone mineralization, weight gain, muscle weakness, hyperglycemia, and hypertension.

5.3 Elevated Blood Pressure, Salt and Water Retention, and Hypokalemia
Acthar Gel can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. Dietary salt restriction and potassium supplementation may be necessary. Caution should be used in the treatment of patients with hypertension, congestive heart failure, or renal insufficiency.

5.4 Vaccination
Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel. Killed or inactivated vaccines may be administered; however, the response to such vaccines can not be predicted. Other immunization procedures should be undertaken with caution in patients who are receiving Acthar Gel, especially when high doses are administered, because of the possible hazards of neurological complications and lack of antibody response.

5.5 Masking Symptoms of Other Diseases
Acthar Gel often acts by masking symptoms of other diseases/disorders without altering the course of the other disease/disorder. Patients should be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight and fecal blood loss.

5.6 Gastrointestinal Perforation and Bleeding
Acthar Gel can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Signs of gastrointestinal perforation, such as peritoneal irritation, may be masked by the therapy. Use caution where there is the possibility of impending perforation, abscess or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer.

5.7 Behavioral and Mood Disturbances
Use of Acthar Gel may be associated with central nervous system effects ranging from euphoria, insomnia, irritability (especially in infants), mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated. These effects are reversible once Acthar Gel therapy is stopped.

5.8 Comorbid Diseases
Patients with a comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar Gel in patients with diabetes and myasthenia gravis.

5.9 Ophthalmic Effects
Prolonged use of Acthar Gel may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi and viruses.

5.10 Immunogenicity Potential
Acthar Gel is immunogenic. Limited available data suggest that a patient may develop antibodies to Acthar Gel after chronic administration and loss of endogenous ACTH and Acthar Gel activity. Prolonged administration of Acthar Gel may increase the risk of hypersensitivity reactions. Cases of anaphylaxis have been reported in the postmarketing setting. Use in patients with sensitivity to porcine protein is contraindicated, and the possibility of sensitivity should be considered during the course of treatment should symptoms arise.

5.11 Use in Patients with Hypothyroidism or Liver Cirrhosis
There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver.

5.12 Negative Effects on Growth and Physical Development
Long-term use of Acthar Gel may have negative effects on growth and physical development in pediatric patients. Changes in appetite are seen with Acthar Gel therapy, with the effects becoming more frequent as the dose or treatment period increases. These effects are reversible once Acthar Gel therapy is stopped. Growth and physical development of pediatric patients on prolonged therapy should be carefully monitored.

5.13 Decrease in Bone Density
Decrease in bone formation and an increase in bone resorption both through an effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function may occur. These, together with a decrease in the protein matrix of the bone (secondary to an increase in protein catabolism) and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and to the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating therapy, and bone density should be monitored in patients on long term therapy.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Infections *[see Warnings and Precautions (5.1)]*
- Cushing's Syndrome and Adrenal Insufficiency Upon Withdrawal *[see Warnings and Precautions (5.2)]*
- Elevated Blood Pressure, Salt and Water Retention, and Hypokalemia *[see Warnings and Precautions (5.3)]*
- Masking Symptoms of Other Diseases *[see Warnings and Precautions (5.5)]*

- Gastrointestinal Perforation and Bleeding *[see Warnings and Precautions (5.6)]*
- Behavioral and Mood Disturbances *[see Warnings and Precautions (5.7)]*
- Ophthalmic Effects *[see Warnings and Precautions (5.9)]*
- Immunogenicity Potential *[see Warnings and Precautions (5.10)]*
- Negative Effects on Growth and Physical Development *[see Warnings and Precautions (5.12)]*
- Decrease in Bone Density *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

Adverse Reactions in Infants and Children Under 2 Years of Age

While the types of adverse reactions seen in infants and children under age 2 treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Below is a summary of adverse reactions specifically tabulated from source data derived from retrospective chart reviews and clinical trials in children under 2 years of age treated for infantile spasms. The number of patients in controlled trials at the recommended dose was too few to provide meaningful incidence rates or to permit a meaningful comparison to the control groups. The most common adverse reactions (5% or greater in the recommended twice daily dosing group) for the treatment of infantile spasms are increased risk of infections, convulsions, hypertension, irritability, and pyrexia.

TABLE: Incidence (%) of Adverse Reactions Occurring in ≥2% of Infants and Children Under 2 Years of Age Treated with Acthar Gel

Adverse Reactions	Recommended 75 U/m² twice daily n=122, (%)	150 U/m² once daily n=37 (%)
Cardiac disorders		
Cardiac Hypertrophy	3	0
Endocrine disorders		
Cushingoid	3	22
Gastrointestinal disorders		
Diarrhea	3	14
Vomiting	3	5
Constipation	0	5
General disorders and administration site conditions		
Irritability	7	19
Pyrexia	5	8
Infections and infestations		
Infection*	20	46
Investigations		
Weight gain	1	3
Metabolism and nutrition disorders		
Increased appetite	0	5
Decreased appetite	3	3
Nervous system disorders		
Convulsion†	12	3
Respiratory, thoracic and mediastinal disorders		
Nasal Congestion	1	5
Skin and subcutaneous tissue disorders		
Acne	0	14
Rash	0	8
Vascular disorders		
Hypertension	11	19

*Specific infections that occurred at ≥ 2% were candidiasis, otitis media, pneumonia and upper respiratory tract infections. †In the treatment of infantile spasms, other types of seizures/convulsions may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally, the spasms sometimes mask other seizures and once the spasms resolve after treatment, the other seizures may become visible.

These adverse reactions may also be seen in adults and children over 2 years of age when treated for other purposes and with different doses and regimens.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Acthar Gel.

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergic Reactions

Allergic responses have presented as dizziness, nausea, and anaphylaxis (anaphylactic shock, hypotension, respiratory compromise, urticaria, edema).

Cardiovascular

Necrotizing angitis (adults only), congestive heart failure, atrial fibrillation, and palpitations.

Dermatologic

Skin thinning (adults only), facial erythema, and increased sweating (adults only).

Endocrine

Decreased carbohydrate tolerance (infants only), hirsutism, and menstrual irregularities.

Gastrointestinal

Pancreatitis (adults only), abdominal distention, and ulcerative esophagitis.

General Disorders and Administration Site Conditions

Injection site reaction and asthenic conditions (including fatigue, malaise, asthenia, and lethargy).

Infections and Infestations

Abscess.

Investigations

Blood glucose increased.

Metabolic

Hypokalemic alkalosis (infants only) and fluid retention (including peripheral swelling).

Musculoskeletal

Muscle weakness and vertebral compression fractures (infants only).

Neurological

Headache (adults only), vertigo (adults only), subdural hematoma, intracranial hemorrhage (adults only), and reversible brain shrinkage (usually secondary to hypertension) (infants only).

Psychiatric Disorders

Insomnia.

6.3 Possible Additional Steroidogenic Effects

Based on steroidogenic effects of Acthar Gel certain adverse events may be expected due to the pharmacological effects of corticosteroids. The adverse events that may occur but have not been reported for Acthar Gel are:

Dermatologic

Impaired wound healing, petechiae and ecchymoses, and suppression of skin test reactions.

Metabolic

Negative nitrogen balance due to protein catabolism and alteration in glucose tolerance.

Musculoskeletal

Loss of muscle mass and aseptic necrosis of femoral and humeral heads.

Neurological

Increased intracranial pressure with papilledema, (pseudo-tumor cerebri) usually after treatment, and subdural effusion.

Ophthalmic

Exophthalmos.

7 DRUG INTERACTIONS

Formal drug-drug interaction studies have not been performed.

Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on Acthar Gel's pharmacological effect of stimulating an endogenous steroid response *[see Clinical Pharmacology (12.1)]*, Acthar Gel may cause fetal harm when administered to a pregnant woman. The published literature on systemic corticosteroid use during pregnancy, which may be relevant, suggests potential concerns. Intrauterine growth restriction, decreased birth weight, and preterm birth have been reported with maternal use of corticosteroids; however, the underlying maternal condition may also contribute to these risks. Hypoadrenalism has also been reported in infants after high-dose and/or long-term use of corticosteroids during pregnancy *(see Clinical Considerations)*. The potential adverse developmental effects of Acthar Gel have not been adequately assessed in animals.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal-Neonatal Adverse Reactions

Hypoadrenalism has been reported in infants born to mothers treated with systemic corticosteroids during pregnancy. Infants born to mothers treated with Acthar Gel should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly *[see Warnings and Precautions (5.2)]*.

8.2 Lactation

Risk Summary

There are no available data on the presence of corticotropin in either human or animal milk, the effects on the breastfed infant, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Acthar Gel and any potential adverse effects on the breastfed infant from Acthar Gel or from the underlying maternal condition.

8.4 Pediatric Use

Acthar Gel is indicated as monotherapy for the treatment of infantile spasms in infants and children less than 2 years of age. Both serious and other adverse reactions can occur in this population *[see Warnings and Precautions (5) and Adverse Reactions (6.1)]*.

The efficacy of Acthar Gel for the treatment of infantile spasms in infants and children less than 2 years of age was evaluated in a randomized, single blinded (video EEG interpreter blinded) clinical trial and an additional active control supportive trial *[see Clinical Studies (14)]*. A responding patient was defined as having both complete cessation of spasms and elimination of hypsarrhythmia.

Safety in the pediatric population for infantile spasms was evaluated by retrospective chart reviews and data from non-sponsor conducted clinical trials *[see Adverse Reactions (6.1)]*. While the types of adverse reactions seen in infants and children under 2 years of age treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Effects on growth are of particular concern *[see Warnings and Precautions (5.12)]*. Serious adverse reactions observed in adults may also occur in children *[see Warnings and Precautions (5)]*.

11 DESCRIPTION

Acthar Gel is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides. The Acthar Gel manufacturing process converts the initial porcine pituitary extract with low ACTH content into a mixture having modified porcine ACTH and other related peptide analogs solubilized in gelatin. A major component in the formulated complex mixture is N-25 deamidated porcine ACTH (1-39).

Acthar Gel is supplied as a sterile preparation in 16% gelatin to provide a prolonged release after intramuscular or subcutaneous injection. Acthar Gel also contains 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of Acthar Gel in the treatment of infantile spasms is unknown.

Acthar Gel and endogenous ACTH stimulate the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. Prolonged administration of large doses of Acthar Gel induces hyperplasia and hypertrophy of the adrenal cortex and continuous high output of cortisol, corticosterone and weak androgens. The release of endogenous ACTH is under the influence of the nervous system via the regulatory hormone released from the hypothalamus and by a negative corticosteroid feedback mechanism. Elevated plasma cortisol suppresses ACTH release.

Acthar Gel is also reported to bind to melanocortin receptors.

The trophic effects of endogenous ACTH and Acthar Gel on the adrenal cortex are not well understood beyond the fact that they appear to be mediated by cyclic AMP.

12.3 Pharmacokinetics

ACTH rapidly disappears from the circulation following its intravenous administration; in people, the plasma half-life is about 15 minutes. The pharmacokinetics of Acthar Gel have not been adequately characterized.

The maximal effects of a trophic hormone on a target organ are achieved when optimal amounts of hormone are acting continuously. Thus, a fixed dose of Acthar Gel will demonstrate a linear increase in adrenocortical secretion with increasing duration for the infusion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Adequate studies of the carcinogenic potential of Acthar Gel have not been conducted.

Mutagenesis

The genotoxic potential of Acthar Gel has not been adequately evaluated.

Impairment of Fertility

The potential effects of Acthar Gel on fertility have not been adequately assessed in animals.

14 CLINICAL STUDIES

The effectiveness of Acthar Gel as a treatment for infantile spasms was demonstrated in a single blinded (video EEG interpreter blinded) clinical trial in which patients were randomized to receive either a 2 week course of treatment with Acthar Gel (75 U/m^2 intramuscular twice daily) or prednisone (1 mg/kg by mouth twice daily). The primary outcome was a comparison of the number of patients in each group who were treatment responders, defined as a patient having complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG performed 2 weeks following treatment initiation, rated by an investigator blinded to treatment. Thirteen of 15 patients (86.7%) responded to Acthar Gel as compared to 4 of 14 patients (28.6%) given prednisone ($p<0.002$). The 2-week treatment was followed by a 2-week period of taper. Nonresponders to the prednisone treatment were eligible to receive Acthar Gel treatment. Seven of 8 patients (87.5%) responded to Acthar Gel after not responding to prednisone. Similarly, the 2 nonresponder patients from the Acthar Gel treatment were eligible to receive treatment with prednisone. One of the 2 patients (50%) responded to the prednisone treatment after not responding to Acthar Gel.

A supportive single-blind, randomized clinical trial comparing high-dose, long-duration treatment (150 U/m^2 once daily for 3 weeks, n=30) of Acthar Gel with low-dose, short-duration treatment (20 U once daily for 2 weeks, n=29) for the treatment of infantile spasms was also evaluated in infants and children less than 2 years of age. Nonresponders (defined as in the previously described study) in the low-dose group received a dose escalation at 2 weeks to 30 U once daily. Nominal statistical superiority of the high dose treatment, as compared to the low dose treatment, was observed for cessation of spasms but not for the resolution of hypsarrhythmia.

16 HOW SUPPLIED/STORAGE AND HANDLING

Acthar Gel (repository corticotropin injection) is supplied as 5 mL multi-dose vial (NDC 63004-8710-1) containing 80 USP Units per mL. Acthar Gel (repository corticotropin injection) should be warmed to room temperature before using. Do not over pressurize the vial prior to withdrawing the product.

Store Acthar Gel (repository corticotropin injection) under refrigeration between 2°C to 8°C (36°F to 46°F). Product is stable for the period indicated on the label when stored under the conditions described.

17 PATIENT COUNSELING INFORMATION

Advise caretakers of patients with infantile spasms to read the FDA-approved patient labeling (Medication Guide).

Patients should be instructed to take Acthar Gel only as prescribed. They should not stop treatment suddenly unless instructed by their healthcare provider to do so.

Patients, their caregivers and families should be advised as to the importance of the need for careful monitoring while on and during titration from Acthar Gel treatment and the importance of not missing scheduled doctor's appointments.

Infections

Advise patients, their caregivers, and families to contact their healthcare provider if the patient develops an infection or fever. Inform patients and caregivers that a fever may not necessarily be present during infection and to try to limit contact with other people with infections to minimize the risk of infection while taking Acthar Gel *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Cushing's Syndrome and Adrenal Insufficiency Upon Withdrawal

Advise patients to contact their healthcare provider if they develop signs or symptoms of Cushing's Syndrome, such as fat increases in the face (moon face) or trunk area, cutaneous striae, easy bruisability, weight gain, muscle weakness, hyperglycemia, and hypertension *[see Warnings and Precautions (5.2)]*.

Inform patients that adrenal insufficiency can occur upon withdrawal of Acthar Gel. Advise patients to contact their healthcare provider if they develop weakness, hyperpigmentation, weight loss, hypotension, or abdominal pain. Advise caregivers of patients with infantile spasms that symptoms of adrenal insufficiency may be difficult to identify and that additional symptoms may include anorexia, fatigue, or lethargy *[see Warnings and Precautions (5.2)]*.

Elevated Blood Pressure, Salt and Water Retention, and Hypokalemia

Advise patients, their caregivers and families to contact their healthcare provider if the patient experiences an increase in blood pressure or water retention *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

Vaccinations

Advise patients and caregivers of patients to not to be vaccinated with live or live attenuated vaccines during treatment with Acthar Gel. Additionally, other immunization procedures in patients or in family members who will be in contact with the patient should be undertaken with caution while the patient is taking Acthar Gel *[see Warnings and Precautions (5.4)]*.

Masking Symptoms of Other Diseases

Inform patients, their caregivers, and families that Acthar Gel may mask symptoms of other diseases/disorders without altering the course of the other disease/disorder. Monitor the patient carefully during and for a period following discontinuation of therapy and inform their healthcare provider if signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight, or fecal blood loss occur *[see Warnings and Precautions (5.5)]*.

Gastrointestinal Perforation and Bleeding

Advise patients, their caregivers and families to contact their healthcare provider if the patient or the caregiver notices blood or a change in color of the patient's stool *[see Warnings and Precautions (5.6)]*.

Behavioral and Mood Disturbances

Inform patients, their caregivers and families that signs of irritability, sleep disturbances, mood swings, personality changes, or severe depression may occur. These effects are reversible once Acthar Gel therapy is stopped *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1)]*.

Negative Effects on Growth and Physical Development

Advise patients, their caregivers and families that changes in appetite, most often leading to weight gain, are seen with Acthar Gel therapy, becoming more frequent as the dose or treatment period increases. These effects are reversible once Acthar Gel therapy is stopped *[see Warnings and Precautions (5.12) and Adverse Reactions (6.1)]*.

Decrease in Bone Density

Advise patients, their caregivers and families that prolonged use of Acthar Gel may inhibit skeletal growth in children and adolescents, and may cause osteoporosis and decreased bone density at any age. If prolonged use is necessary, Acthar Gel should be given intermittently along with careful observation *[see Warnings and Precautions (5.13) and Adverse Reactions (6.1)]*.

Infantile Spasms Additional Information

Inform caregivers that, in the treatment of infantile spasms, other types of seizures may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment with Acthar Gel, the other seizures may become visible. Advise parents and caregivers to inform the patient's healthcare provider of any new onset of seizures so that appropriate management can then be instituted *[see Adverse Reactions (6.1)]*.

Pregnancy

Advise pregnant women of the potential risk to a fetus *[see Use in Specific Populations (8.1)]*.

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US-2101218
PL065 Rev.10/2021

Mallinckrodt™ Pharmaceuticals