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/m² divided into twice daily intramuscular injections of 75 U/m². 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)

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

--- 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), insomnias, headache, and blood glucose increased. (6.2)

--- 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: 06/2023

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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, choroidneuritis; anterior segment inflammation.

1.8 Respiratory Diseases
Symptomatic sarcoidosis.

1.9 Edematous Diseases
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/m2 (divided into twice daily intramuscular injections of 75 U/m2) 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/m2 in the morning for 3 days; 15 U/m2 in the morning for 3 days; 10 U/m2 in the morning for 3 days; and 10 U/m2 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

\[ BSA(m^2) = \sqrt{\frac{weight (kg) \times height (cm)}{3600}} \]

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 tuberculosis reactivity should be observed closely, and if therapy is prolonged, bacterial, fungal, protozoan or helminthic infections. Patients with latent tuberculosis or tuberculin reactivity should be observed closely, and if therapy is prolonged, their 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 Cushings’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 bruising, 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 may 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 Immunogenic 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 possibly increasing when the patient is already overweight or obese. Children with idiopathic or steroid-responsive growth failure may have unfavorable growth effects with prolonged use of Acthar Gel. For children, a growth retardation monitoring program is recommended. The patient’s growth rate should be monitored at frequent intervals, and the physician should consider special dietary measures in children at risk for growth retardation. Physical development changes may be expected in children treated with Acthar Gel. Adverse effects 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)].

5.13 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)]
• Immune Genicity 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**

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

*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 the boy and the dosage regimen. Effects on growth are of particular concern [see Warnings and Precautions (5)]. 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 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 hypertrrophy 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/mL 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 who had a reduction in seizure frequency of 50% or more and a minimum of 7 days of treatment. Seventeen of 21 patients (80.0%) responded to Acthar Gel treatment for 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 overpressurize 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.