ACTHAR FOR INFANTILE SPASMS

Injection Treatment Tracker Calendar

What is Acthar Gel?
Acthar® Gel (repository corticotropin injection) is a prescription medicine that is used to treat infantile spasms in infants and children under 2 years of age.

Acthar is given as an injection into the muscle. Do not inject it under the skin, into a vein, or give it to your child by mouth.

SELECT IMPORTANT SAFETY INFORMATION
DO NOT take Acthar until you have talked to your doctor if you have any of the following conditions:

- A skin condition called scleroderma
- Bone density loss or osteoporosis
- Any infections, including fungal, bacterial, or viral
- Eye infections, such as ocular herpes simplex
- Had recent surgery
- Stomach ulcers or a history of stomach ulcers
- Heart failure
- Uncontrolled high blood pressure
- Allergies to pig-derived proteins
- Have been given or are about to receive a live or live attenuated vaccine
- Suspected congenital infections (in children under 2 years of age)
- If you have been told that you have Cushing’s syndrome or Addison’s disease

Please see additional Important Safety Information inside as well as accompanying full Prescribing Information and Medication Guide.
Getting started

Preparing Acthar

- Remove the vial of Acthar from the refrigerator
  - Let it sit for 15 to 30 minutes to reach room temperature.
  - You can roll it in the palms of your hands or hold it under your arm during the warming process
- Wash your hands
- For a video demonstration on how to properly inject your child, please view our injection training video at www.ActharInjectionTraining.com.

Materials Needed for Injection

1. Vial of Acthar
2. Drawing Needle (20 G)
3. Injection Needle (23 G)*
4. Syringe
5. Alcohol Wipes
6. Sterile Gauze Pad
7. Sharps Container

*Please use the injection needle size as instructed by your healthcare provider.

Use the Treatment Tracker Calendar to keep track of your child’s treatment schedule and progress.

Follow the treatment schedule provided by your doctor

- The treatment calendar tracks when you gave Acthar treatment, at what dose, and where the injection was given
- The dose may change over time, and injections are given in different parts of the thigh. It is helpful to record this information on the Treatment Tracker Calendar to share with your doctor

The treatment calendar is an example of the most common injection schedule. Always follow your doctor’s instructions.

Please see Important Safety Information inside as well as accompanying full Prescribing Information and Medication Guide.

### My Treatment Tracker Calendar

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Injection in 6 Steps

1. Lay child flat on back or hold in your lap with child’s leg between yours

2. Find the thickest portion of the thigh muscle, which is the middle third (between the knee and uppermost point of the thighbone) on the outer side

3. Clean the area to be injected with an alcohol swab, let dry, then use the thumb and forefinger of the hand not holding the syringe to stretch or pinch together the skin

4. Use the 20-gauge needle to draw Acthar into syringe, replace the needle cap, detach the needle, and attach the 23-gauge needle for injection, or as instructed by your healthcare provider

5. Hold the syringe like a pencil or dart and, using a quick motion, insert the needle at a 90° angle through the skin

6. Slowly push the plunger in until the syringe is empty, then pull straight out

This quick reference guide is not intended to replace the injection training that you received from your doctor or nurse. This injection summary is intended to complement, and be used in conjunction with, the Acthar Step-by-Step Injection Guide and instructional video. Remember, your doctor or nurse is always the best source of advice. You can also visit www.ActharIS.com for written injection instructions, an instructional injection video, and additional information. Prior to injecting Acthar, please refer to the full Prescribing Information and Medication Guide accompanying this Step-by-Step Injection Guide, or the Important Safety Information in this document. Speak with your doctor about the potential side effects associated with Acthar.

IMPORTANT SAFETY INFORMATION

DO NOT take Acthar until you have talked to your doctor if you have any of the following conditions:

- A skin condition called scleroderma
- Bone density loss or osteoporosis
- Any infections, including fungal, bacterial, or viral
- Eye infections, such as ocular herpes simplex
- Had recent surgery
- Stomach ulcers or a history of stomach ulcers
- Heart failure
- Uncontrolled high blood pressure
- Allergies to pig-derived proteins
- Have been given or are about to receive a live or live attenuated vaccine
- Suspected congenital infections (in children under 2 years of age)
- If you have been told that you have Cushing’s syndrome or Addison’s disease

Tell your doctor about any other health problems that you have. Give your doctor a complete list of medicines you are taking. Include all nonprescription medicines, vitamins, and herbal supplements that you are taking.

What is the most important information I should know about Acthar?

- Never inject Acthar directly into a vein, under the skin, or give it to your child by mouth
- Always inject Acthar into the muscle
- Follow your doctor’s instructions for injecting Acthar
- Never stop treatment suddenly unless your doctor tells you to do so
- Try not to miss any scheduled doctor’s appointments. It is important for the doctor to monitor you while taking Acthar
**Acthar and corticosteroids have similar side effects.**

- You may be more likely to get new infections. Also, old infections may become active. Tell your doctor if you see any signs of an infection. Contact your doctor at the first sign of an infection or fever. Signs of infection are fever, cough, vomiting, or diarrhea. Other signs may be flu or any open cuts or sores.
- When taking Acthar long term, your adrenal gland may produce too much of a hormone called cortisol. This can result in symptoms of Cushing’s syndrome. This may cause increased upper body fat, a rounded “moon” face, bruising easily, or muscle weakness.
- Sometimes when you stop taking Acthar long term, your body may not produce enough natural cortisol. This is called “adrenal insufficiency.” Your doctor may prescribe a steroid medicine to protect you until the adrenal gland recovers.
- You might develop high blood pressure, or retain too much fluid. As a result of this, your doctor may recommend some changes to your diet, such as eating less salt and taking certain supplements.
- Vaccines may not work well when you are on Acthar. Talk to your doctor about which vaccines are safe to use when you are taking Acthar.
- Acthar may hide symptoms of other diseases. This can make it more difficult for your doctor to make a diagnosis if something else is going on.
- Stomach or intestinal problems. Acthar may increase the risk of bleeding stomach ulcers. Tell your doctor if you have stomach pains, bloody vomit, bloody or black stools, excessive tiredness, increased thirst, difficulty breathing, or increased heart rate.
- Taking Acthar can make you feel irritable or depressed. You may also have mood swings or trouble sleeping.
- If you have other conditions, such as diabetes or muscle weakness, you may find they get worse.
- You might develop certain eye conditions, such as cataracts, glaucoma, or optic nerve damage.
- Your body may develop allergies to Acthar. Signs of allergic reaction are:
  - Skin rash and itching
  - Swelling of the face, tongue, lips, or throat
  - Trouble breathing
- Long-term Acthar use can affect growth and physical development in children. This can be reversed when Acthar is no longer needed.
- Acthar may cause osteoporosis (weak bones).
- Acthar should not be given to adults who are pregnant or plan to become pregnant.

**What are the most common side effects of Acthar?**

The most common side effects of Acthar are similar to those of steroids. They include:

- Fluid retention
- High blood sugar
- High blood pressure
- Behavior and mood changes
- Changes in appetite and weight

Specific side effects in children under 2 years of age include:

- Increased risk of infections
- High blood pressure
- Irritability
- Symptoms of Cushing’s syndrome
- Thickening of the heart muscle (cardiac hypertrophy)
- Weight gain

The above side effects may also be seen in adults and children over 2 years of age.

**These are not all of the possible side effects of Acthar.**

Tell your doctor about any side effect that bothers you, or that does not go away. Call your doctor or pharmacist for medical advice about side effects. You may report side effects to the FDA. Call 1-800-FDA-1088 or visit www.fda.gov/medwatch. You may also report side effects by calling 1-800-844-2830.

**Please see accompanying full Prescribing Information.**

For parents and caregivers of IS patients, please also see accompanying Medication Guide.
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) INJECTION, GEL for INTRAMUSCULAR I SUBCUTANEOUS use

Initial U.S. Approval: 1952

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CONTRAINDICATIONS

- Acthar Gel is indicated for the treatment of infantile spasms in infants and children under 2 years of age. (1.1)
- Acthar Gel is contraindicated in patients receiving immunosuppressive doses of corticosteroids, 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)
- Acthar Gel is contraindicated in children under 2 years of age with suspected congenital infections. (4)

DOSE FORMS AND STRENGTHS

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

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INFECTIONS: Increased susceptibility to new infection and increased risk of exacerbation, (5.1)

TREATMENT of conditions listed within the INDICATIONS AND USAGE section is recommended. (4)

ACTHAR GEL is contraindicated in children under 2 years of age with suspected congenital infections. (5.1)

ACTHAR GEL may be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; and edematous state. (1.3 to 1.9)

DOSE 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)

DOSE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Acthar Gel should never be given intravenously. (2.1)
- Acthar Gel 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, or sensitivity to proteins of porcine origin. (4)

ADMINISTRATION of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. (4)

TREATMENT of conditions listed within the INDICATIONS AND USAGE section is contraindicated when they are accompanied by primary adrenocortical insufficiency or adrenocortical hyperfunction. (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-axis suppression after stopping treatment. (5.2)

5.2 Cushing’s Syndrome and Adrenal Insufficiency Upon Withdrawal
5.3 Elevated Blood Pressure, Salt and Water Retention and Hypokalemia
5.4 Vaccination
5.5 Masking of Symptoms of Other Underlying Disease/Disorders
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5.10 Immunogenicity Potential
5.11 Use in Patients with Hypothyroidism or Liver Cirrhosis
5.12 Negative Effects on Growth and Physical Development
5.13 Decrease in Bone Density
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ADVERSE REACTIONS

- Common adverse reactions for Acthar Gel 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. (6)

- Specific adverse reactions resulting from drug use in children under 2 years of age are increased risk of infections, hypertension, irritability, Cushingoid symptoms, cardiac hypertrophy and weight gain. (6.1.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt at 1-800-778-7898 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Use in Specific Populations

- Pregnancy: Acthar Gel 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. (8.1)

- 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 and 8.4)

See 17 for Patient Counseling Information and FDA-approved Medication Guide

Revised: 3/2019

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*Sections or subsections omitted from the full prescribing information are not listed.
Acthar Gel 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 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 might be expected to occur [see Adverse Reactions (6.3)].

5.1 Infections

Adverse events following the use of live vaccines with Acthar Gel may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic infections. Patients with latent tuberculous 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 hypophysal-pituitary-axis (HPA) 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 characteristic 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 extracellular potassium. 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 impeding 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.

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 hypertension, salt and water retention, and increased extracellular potassium.

5.9 Ophthalmic Effects

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

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. Sensitivity to porcine protein should be considered before starting therapy and 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 children. 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.

5.14 Use in Pregnancy
Acthar Gel has been shown to have an embryocidal effect. Apprise women of potential harm to the fetus [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

Please refer to Adverse Reactions in Infants and Children Under 2 Years of Age (Section 6.1.1) for consideration when treating patients with Infantile Spasms. The adverse reactions presented in Section 6.2 are primarily provided for consideration in use in adults and in children over 2 years of age, but these adverse reactions should also be considered when treating infants and children under 2 years of age.

Acthar Gel causes the release of endogenous cortisol from the adrenal gland. Therefore all the adverse effects known to occur with elevated cortisol may occur with Acthar Gel administration as well. Common adverse reactions include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

6.1 Clinical Studies 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.

6.1.1 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 condition, 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.

TABLE: Incidence (%) of Treatment Emergent Adverse Events Occurring in ≥ 2% of Acthar Gel (repository corticotropin injection) Infants and Children under 2 Years of Age

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Recommended 75 U/m² bid n=122, (%)</th>
<th>150 U/m² qd n=37 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>* 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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 associated with the use of Acthar Gel have been identified from postmarketing experience with Acthar Gel. Only adverse events that are not listed above as adverse events reported from retrospective chart reviews and non-sponsor conducted clinical trials and those not discussed elsewhere in labeling, are listed in this section. Because the adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to use with Acthar Gel. Events are categorized by system organ class. Unless otherwise noted these adverse events have been reported in infants, children and adults.

6.2.1 Allergic Reactions
Allergic responses have presented as dizziness, nausea and shock (adults only).

6.2.2 Cardiovascular
Necrotizing angitis (adults only) and congestive heart failure.

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

6.2.4 Endocrine
Decreased carbohydrate tolerance (infants only) and hirsutism.

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

6.2.6 General Disorders and Administration Site Conditions
Injection site reactions.

6.2.7 Metabolic
Hypokalemic alkalosis (infants only).

6.2.8 Musculoskeletal
Muscle weakness and vertebral compression fractures (infants only).

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

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:

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

6.3.2 Endocrine
Menstrual irregularities.

6.3.3 Metabolic
Negative nitrogen balance due to protein catabolism.

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

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

6.3.6 Ophthalmologic
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
Pregnancy Class C: Acthar Gel has been shown to have an embryocidal effect. There are no adequate and well-controlled studies in pregnant women. Acthar Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Acthar Gel, when treating a nursing mother, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk and benefit to the mother.
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 in this population are discussed in Warnings and Adverse Reactions in Infants and Children Under 2 Years of Age [see Sections 5 and 6.1.1]. 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 interpreted 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 (6.1.1)]. 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)].

10 OVERDOSAGE
While chronic exposure to Acthar Gel at high doses can be associated with a variety of potential serious adverse effects, it is not expected that a single high dose, or even several large doses, will have the potential for serious adverse effects compared to a standard dose. There have been no reports of death or acute overdose symptoms from Acthar Gel in clinical studies or in the published literature.

The intramuscular route of administration makes it unlikely that an inadvertent acute overdose will occur. The typical daily dose of Acthar Gel to treat an infant that has a BSA of 0.4 m² would be 60 U/day. Using the 1-cc syringe supplied with Acthar Gel, the maximum amount that can be injected is 80 Unijection, which is a well-tolerated single dose.

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 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. Endogenous corticosteroids suppress 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. 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
Adequate and well-controlled studies have not been done in animals. Human use has not been associated with an increase in malignant disease [see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)].

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/m² 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/m² 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 (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° to 8°C (36° to 46°F). Product is stable for the period indicated on the label when stored under the conditions described.

17 PATIENT COUNSELING INFORMATION
Caregivers of patients with infantile spasms should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to administering Acthar Gel. Patients should be instructed to take Acthar Gel only as prescribed. They should not stop treatment suddenly unless instructed by their physician 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.

Patients, their caregivers and families should be advised that if the patient develops an infection, they should contact their physician. They should be educated that a fever may not necessarily be present during infection. The patient should also 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 (6.1.1)].

Patients, their caregivers and families should be advised that if the patient experiences an increase in blood pressure they should contact their physician [see Warnings and Precautions (5.1) and Adverse Reactions (6.1.1)].

Patients, their caregivers and families should be advised that the patient may be monitored for signs of adrenal insufficiency such as weakness, fatigue, lethargy, anorexia, weight loss, hypotension, abdominal pain or hyperpigmentation, 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 (5.7) and Adverse Reactions (6.1.1)].

Patients, their caregivers and families should be advised that the patient may be monitored for signs of adrenal insufficiency such as weakness, fatigue, lethargy, anorexia, weight loss, hypotension, abdominal pain or hyperpigmentation after treatment has stopped. Since the recovery of the adrenal gland varies from days to months, patients may need to be protected from the stress of trauma or surgery by the use of corticosteroids during the period of stress [see Warnings and Precautions (5.2)].

Patients should be advised not to be vaccinated with live or killed 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)].

Patients, their caregivers and families should be advised that prolonged use of Acthar Gel in children may result in Cushings syndrome and associated adverse reactions, may inhibit skeletal growth, and may cause osteoporosis and decreased bone density. If prolonged use is necessary, Acthar Gel should be given intermittently along with careful observation [see Warnings and Precautions (5.2), (5.12), and (5.13) and Adverse Reactions (6.1.1)].

Patients, their caregivers and families should be informed that Acthar Gel may mask symptoms of other diseases/disorders without altering the course of the other disease/disorder. The patient may need to be monitored during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypotension, hyperglycemia, change in body weight, and fecal blood loss [see Warnings and Precautions (5.5)].

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. Patients and parents should inform their physician of any new onset of seizures so that appropriate management can then be instituted [see Adverse Reactions (6.1.1)].

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