Getting started with Acthar

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.

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 on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
**Acthar® Gel**
(repository corticotropin injection) [AK-thar jel]

**What is Acthar Gel?**
Treatment of 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**
You should **NOT** take Acthar before talking to your doctor if you have any of these conditions: A skin condition called scleroderma, bone density loss, any infections, herpes simplex of the eye, had recent surgery, stomach ulcers or history of stomach ulcers, heart failure, uncontrolled high blood pressure, have been given, or are about to receive, a live or live attenuated vaccine, or have allergies to pig-derived protein. Tell your doctor if you are pregnant or plan on becoming pregnant.

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.

Acthar can cause side effects similar to those with steroid treatments. It can cause adrenal gland changes which may cause symptoms of Cushing’s syndrome.

People on steroids or with Cushing’s syndrome may experience: increased risk of infections; an increase in upper body fat, rounded “moon” face, bruising easily, or muscle weakness; increased blood pressure, body salt, and fluid; unpredictable response to vaccines; stomach or intestinal problems; changes in mood or behavior; worsening of other medical conditions; eye problems; or allergic reactions. Tell your doctor if you experience any of the above symptoms. Also tell your doctor about any other health problems you have and about all medicines you are taking.

Taking Acthar may mask symptoms of other diseases and may cause bone density loss at any age.

The most common side effects include: Fluid retention, changes in blood sugar, increased blood pressure, behavior and mood changes, and changes in appetite and weight.

Specific side effects in children under 2 years of age include: Increased risk of infections, increased blood pressure, irritability, symptoms of Cushing’s syndrome, cardiac hypertrophy (thickening of the heart muscle) and 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 additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
Learn how to inject Acthar

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.

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
Get started with Acthar

Your kit contains information about infantile spasms (IS) and how to inject Acthar.

- Learn About Acthar Brochure
- Step-by-Step Injection Guide
- Treatment Tracker Calendar
- Materials Organization Mat
Getting started with Acthar

Once you receive Acthar:

1. Check the expiration date on the Acthar vial to make sure you are using it before the date listed

2. Prior to each use, check for any signs of contamination (cloudiness, small flecks, particles, etc)

3. Refrigerate Acthar as soon as you receive it and check that your refrigerator is set between 36°F and 46°F or 2°C and 8°C

4. After puncturing, discard after 28 days

Do not use if:

• The vial is expired
• Any signs of contamination are seen

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
1. ORGANIZE THE INJECTION MATERIALS

You may find it useful to lay the following items on the Materials Organization Mat included in this kit as you prepare to inject Acthar:

- Vial of Acthar
- A 20-gauge needle to use for drawing the medication
- A 23-gauge needle for injecting the medication
- Syringe
- Alcohol swabs
- Sterile gauze pad
- Puncture-resistant container to safely dispose of syringe and needles after use

You will also find included in this kit the Treatment Tracker Calendar to track your child’s treatment schedule and progress.

An injection training video is available in English online at www.ActharInjectionTraining.com. If you have any additional questions, please contact your doctor or healthcare team.

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
2. PREPARE THE INJECTION

• Take the vial of Acthar out of the refrigerator. Recheck the expiration date to make sure the vial has not expired
• 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

Do not inject Acthar immediately after removing from the refrigerator. Let the vial warm to room temperature by leaving it out for 15 to 30 minutes. You can roll it between the palms of your hands or hold it under your arm for a few minutes during the warming process.

• Wash your hands with soap and warm water for at least 20 seconds
• Remove the cap of the vial and use an alcohol swab to wipe the rubber stopper on top of the vial

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
• Attach the 20-gauge needle to the syringe. Before removing the cap of the needle, draw air into the syringe by pulling the syringe plunger to the exact amount your doctor has prescribed (remember to fill in the amount on your Treatment Tracker Calendar once you receive your prescription)

• Remove the needle cap. Insert the needle through the rubber stopper and inject air into the upright vial by pushing down on the plunger until it cannot be pushed farther
While keeping the needle tip in the medication, slowly pull back the plunger to the exact amount your doctor prescribed.

While the syringe is still in the vial, turn vial and syringe upside down.

Keep needle tip in the Acthar at all times when drawing the amount your doctor prescribed.
PREPARE THE INJECTION

- With the tip of the syringe upright and the needle still in the vial, tap the syringe with your finger until any air bubbles rise to the top.
- If bubbles are present, very slowly press the plunger in until only the bubbles are pressed out of the syringe and a droplet starts to form at the needle tip.
- Check that you still have the amount your doctor prescribed in the syringe. If not, place the needle in the gel (medication), draw in the amount you need, and remove bubbles again.

Before injecting, ensure that the needle remains sterile (ie, do not place on a nonsterile surface).

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
After using the 20-gauge needle to draw Acthar into the syringe, replace the needle cap, detach the needle, and attach the thinner (23-gauge) needle.

Remember, the 20-gauge needle is not for injecting. Remove and properly dispose of the 20-gauge needle before attaching the thinner 23-gauge needle to inject with.

Preparation is now complete. Continue to the following sections to learn about injection sites and how to inject Acthar.
3. CHOOSE THE INJECTION SITE

- The injection area is located on the upper outer thigh.
- To locate the correct muscle, start by placing your fingertips on the middle of the thigh and gently press down to locate the thigh bone.
- Run your fingers along the bone toward the hip until you feel a bony protrusion. This is the uppermost point of the thigh bone (see arrow A).
- Now locate the kneecap (see arrow B).
- Divide the distance between these 2 points into thirds.
- The thickest portion of the muscle is in the middle third. Inject into the outer side of the middle third.

Do not inject into the front of the thigh; keep the injection site to the outer side of the muscle.

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
Contact your doctor if you notice any injection-site reactions, including redness, pain, and swelling.

**Injecting the upper outer thigh muscle**
- Common approach for children 0 to 12 months of age; also the preferred site for older children

**Do not inject into:**
- The same site (small area of the muscle) more than once a week
- An area that has skin irritation, including red or swollen areas
- An area that has hardened or is sensitive to touch

Choose the injection site:

1. Injection site 1
2. Injection site 2
3. Injection site 3
4. Injection site 4

Injection area

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You may inject into the same muscle more than once in a day, but rotate the injection sites counterclockwise in that muscle each time, keeping 1 inch between sites.

Keep track of the injections on your Treatment Tracker Calendar.

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Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
4. POSITION YOUR CHILD

• Your child can be lying back flat or held in your lap during the injection, whichever works best
• Remove any clothing around the chosen injection site
• Position the leg so the hip and knee are bent slightly; this will help relax the muscle that will be injected

You also may find it helpful to have another person who can help by:
• Holding your child in the proper position
• Distracting your child with a toy during and after the injection

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
5. PERFORM THE INJECTION

- Clean the area to be injected with an alcohol swab; let the alcohol dry before injecting
- Press the plunger until a droplet forms at the tip of the needle
- Stretch and hold the skin around the injection site between the thumb and fingers of the hand that is not holding the syringe. Steady the muscle by grasping it on each side

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
• Hold the syringe like a pencil or dart with your right hand if you are right-handed and your left if you are left-handed. Using a quick motion, insert the needle at a 90° angle through the skin.

• Slowly push the plunger in until the syringe is empty.

It may be helpful to use a noisy toy to distract and calm your child during and after the injection.
6. COMPLETE THE INJECTION

- Once the syringe is empty, pull the needle straight out. It may be helpful to hold a gauze pad over the injection site and use it to apply pressure once the needle has been removed.
- If there is any blood, wipe it off and, if necessary, apply an adhesive bandage.
- Dispose of the used syringe, needle, and needle cap in a puncture-resistant container. Do not replace the needle cap prior to disposal.
- Wash your hands with soap and warm water.
- Mark the Treatment Tracker Calendar with the injection site location.
- Return the Acthar to the refrigerator (36°F-46°F; 2°C-8°C) between each use.

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
How to dispose of used syringes, needles, and vials

It is important to follow your state and local laws regarding proper disposal of used syringes, needles, and vials. You should be provided a sharps disposal container with your Acthar shipment, but if it is not included, bring your container of used syringes, needles, and vials to your doctor’s office or local hospital for proper disposal.

You should not:

• Reuse syringes, needles, or vials
• Throw the syringes, needles, and vials in household trash
• Recycle syringes, needles, and vials
• Use a clear plastic or glass container for disposal

To make your own sharps container:

• Place used supplies in a heavy plastic or metal container with a tight-fitting lid that is puncture-resistant and leak-proof; you can ask your pharmacist for a sharps container, or you can use a laundry detergent bottle
• Mark “Not for Recycling” on the container
• Reinforce the lid with heavy-duty tape
• Store the container in a secure place out of reach from children or pets
When to call your doctor

Call your doctor right away if any of these potential risks concern you or if your child experiences any of these serious side effects during treatment:

• Increased risk of infections
• Adrenal gland changes
• Increased blood pressure, body salt, and fluid levels
• Unpredictable response to vaccines
• Masking other conditions
• Stomach or intestinal problems
• Changes in mood or behavior
• Worsening of other medical conditions such as diabetes or muscle weakness
• Eye problems
• Allergic reactions
• Problems with growth and physical development
• Bone density loss

Please see additional Important Safety Information on pages 17-19, as well as accompanying full Prescribing Information and Medication Guide.
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
IMPORTANT SAFETY INFORMATION (continued)

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

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

Please see accompanying full Prescribing Information and Medication Guide.
IMPORTANT SAFETY INFORMATION (continued)

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

• 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 use
Initial U.S. Approval: 1952

1 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)

2 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- to 3-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)

3 DOSAGE FORMS AND STRENGTHS
• 5 mL multi-dose vial containing 80 USP units per mL. (3)

4 CONTRAINDICATIONS
• Acthar Gel should never be given intravenously.
• 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.
• Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel.
• Acthar Gel is contraindicated in children under 2 years of age with suspected congenital infections. (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)

5 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)
• 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)
• Vaccination: Do not administer live or live attenuated vaccines to patients on immunosuppressive doses. (5.4)
• 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)
• Use in Pregnancy: Embryocidal effect. Apprise women of potential harm to the fetus. (5.14)

6 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)

7 DRUG INTERACTIONS
• 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
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Infantile spasms
Acthar Gel (repository corticotropin injection) 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 (repository corticotropin injection) 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 reflects 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/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 5 U/m² every other morning for 6 days.

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. Acthar Gel is contraindicated where congenital infections are suspected in infants. Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel.

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 effects may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan or hemlethic infections. Patients with latent tuberculosis or tuberculosis 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 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 while 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 the dose when discontinuing treatment.

Skin 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 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 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.

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. 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 disease, 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 small 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>Hypertension 11 19</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac Hypertrophy 3 0</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Cushingoid 3 22</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation 0 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea 3 14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting 3 5</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Irritability 7 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrexia 5 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infections and infestations</td>
<td>Infection* 20 46</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight gain 1 3</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Increased appetite 0 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased appetite 3 3</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Convulsion† 12 3</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Nasal Congestion 1 5</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Acne 0 14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rash 0 8</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 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.
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].

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 OVERDOSE

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 result in 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 U/inject, 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 with ACTH 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 weak androgenic substances. Prolonged administration of large doses of Acthar Gel induces hyperplasia and hyper trophy 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 hypothalamic portal system and by a negative corticosteroid feedback mechanism. Endogenous plasma corticosteroid 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. 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 (5.14) 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 6 patients (67.5%) 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 over pressurize 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.