Learn about Acthar

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 on pages 12-14, as well as accompanying full Prescribing Information and Medication Guide.
You have just learned your child has a condition called infantile spasms (IS) and has been prescribed Acthar. There is no doubt you have many questions about the disease and treatment for your child.

This brochure is intended to provide information about IS and how treatment with Acthar may help. It may not cover everything you want to know, so after reading this information, write down any questions you have as a reminder to ask your doctor or nurse.

**Here is some Important Safety Information you should know about Acthar:**

- Acthar should never be given to your child subcutaneously (under the skin), intravenously (into a vein), or by mouth. Acthar is given as an injection into the muscle.
- Patients should not receive certain vaccines during Acthar treatment. Talk to your doctor about which vaccines are safe.
- Tell your doctor if your child has: an infection, diabetes, heart problems, kidney problems, stomach or intestinal problems, thyroid problems, liver problems, neuromuscular problems, convulsions or seizures, had exposure to someone with tuberculosis (TB), a previous allergic reaction such as hives, itching, or trouble breathing, to Acthar or pork products, had recent surgery, had a recent vaccination or is scheduled to receive a vaccination, or a family member who is receiving vaccinations. Tell your doctor about all the medicines your child takes, including prescription and non-prescription medicines, vitamins and herbal supplements. Do not start giving a new medicine to your child without first speaking to your doctor.
- These are not all of the Warnings and Precautions for Acthar. Please see full Prescribing Information and pages 12-14 for additional Important Safety Information. For parents and caregivers of IS patients, please also see Medication Guide.

Please see additional Important Safety Information on pages 12-14, as well as accompanying full Prescribing Information and Medication Guide.
What is IS?

IS is a rare and specific type of seizure disorder also known as West syndrome. IS usually begins within the first year of life. Children with IS typically have:

- A specific type of seizure (called spasms)
- A chaotic brain-wave pattern called hypsarrhythmia (hips-a-rith-me-ya)

The spasms are described as sudden, uncontrolled movements of the neck, body, arms, and legs that last only for a few seconds.

You may see the following:

- Repetitive forward head nodding or bobbing
- Bowing from the waist when sitting
- Drawing up of knees when lying down
- Extending or stiffening of the neck, trunk, arms, and legs
- Crossing arms across body as if self-hugging
- Thrusting arms to the side, elbows bent

Spasms are most common during the early morning or when your child wakes up from naps. Often, IS is mistaken for colic. Colic frequently begins at the same time each day. Children with colic will cry, tend to lift their legs repeatedly with their hands clenched, and may have a swollen stomach. It’s important to speak with your doctor about your infant’s spasms.

When making the diagnosis, your doctor may have taken a complete medical history and asked you to describe your child’s spasms. Some parents and caregivers find it helpful to take a video of the child’s spasms and record how often they happen in a journal as soon as they begin. Doctors and nurses may find this information helpful when making the diagnosis and during treatment.

Your doctor may have performed an electroencephalogram (EEG) to determine if your child has hypsarrhythmia. An EEG is a test of brain activity. Children with IS typically have EEGs that show hypsarrhythmia, a chaotic pattern of brain waves.

Please see additional Important Safety Information on pages 12-14, as well as accompanying full Prescribing Information and Medication Guide.
What causes IS?

Once IS is diagnosed, your doctor may run several more tests to try to find out the cause of your child’s IS.

In some children, no cause for IS can be found. This is called cryptogenic, or idiopathic, IS. In most cases, IS is caused by an underlying disease or injury to the brain. Causes could include central nervous system infection, abnormal brain development, or brain injury.

No matter what the cause is, it is important to find and treat IS as quickly and effectively as possible. Be sure to talk to your child’s doctor about the potential effects of IS, as well as the available treatment options and when a follow-up EEG may be appropriate.

How is IS treated?

If children are thought to have IS, they may be sent to an epilepsy center to be diagnosed. Once IS is confirmed, treatment should be started as soon as possible.

The American Academy of Neurology and Child Neurology Society specify that successful treatment must stop both spasms and hypsarrhythmia.

Acthar is one clinically proven therapy that has been shown to help stop spasms and hypsarrhythmia in both children with idiopathic (cryptogenic) IS and those with symptomatic IS, including tuberous sclerosis.

Specific side effects in children under 2 years of age include increased risk of infection, high blood pressure, irritability, symptoms of Cushing’s syndrome, thickening of the heart muscle (cardiac hypertrophy), and weight gain.

LEARN EVEN MORE ABOUT IS AND EXPLORE HELPFUL RESOURCES AT:
www.ActharIS.com
Acthar® Gel (repository corticotropin injection) is a Food and Drug Administration (FDA)-approved medication for IS that contains ACTH (adrenocorticotropic hormone), a naturally occurring hormone, which has been proven to stop spasms and hypsarrhythmia in infants and children under 2 years of age with IS.

How can Acthar help?

Acthar is an FDA-approved treatment for IS that has been shown to help stop both spasms and hypsarrhythmia. Although each child will respond to Acthar differently, in a clinical study, 13 of 15 children (87%) had no spasms and no hypsarrhythmia at week 2.

Side effects such as high blood pressure and high blood sugar were monitored. Irritability and increased appetite were the most frequent side effects, but no infant had to stop or change treatment.

ACTHAR IS PROVEN TO:
• Stop spasms
• Stop hypsarrhythmia

How is Acthar given?

Acthar is given by an intramuscular (into the muscle) injection. Do not inject it under the skin, into a vein, or give it to your child by mouth. Your doctor or nurse should provide detailed instructions about where to give the injection, how much to give, how often, and when to give Acthar to your child. Additionally, the Starter Kit contains a Step-by-Step Injection Guide for your reference. There’s also a video you can watch at www.ActharInjectionTraining.com to help guide you through the injection.

Contact your doctor or nurse if you have any questions about using Acthar.

Please see additional Important Safety Information on pages 12-14, as well as accompanying full Prescribing Information and Medication Guide.
Acthar can cause serious side effects such as 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 including skin rash, swelling of the tongue, lips or throat, or trouble breathing; problems with growth and physical development; enlarged heart; and bone density loss.

The most common side effects of Acthar in infants include: infections, increased blood pressure, irritability and changes in behavior, changes in appetite and weight, diarrhea, and vomiting. Other adverse reactions reported in adults and children over 2 years of age included: abdominal bloating, anxiety, asthma, chest discomfort, congestive heart failure, dizziness, shortness of breath, redness of the face, fluid retention, flushing, headache, injection site pain, tiredness, muscle weakness, nervousness, rapid heart rate, and lack of energy. These are not all of the possible side effects of Acthar. Tell your doctor if your child has any bothersome side effect or side effect that does not go away.

Please see additional Important Safety Information on pages 12-14, as well as accompanying full Prescribing Information and Medication Guide.
Supporting you from prescription through treatment

The Acthar Hub is a no-cost resource provided by Mallinckrodt Pharmaceuticals, the distributor of Acthar. The Acthar Hub provides several support services for Acthar patients. From the moment your child’s doctor prescribes Acthar, you’ll be supported every step of the way.

**INSURANCE SUPPORT**

- The Acthar Hub works directly with your child’s doctor and insurance company to help determine insurance coverage and work through any plan requirements and/or approvals.

**ACTHAR INJECTION TRAINING**

- Schedules injection training with a licensed nurse at home, online, or by phone
- Helps you get comfortable with the injection process

**FINANCIAL ASSISTANCE**

- The Acthar Commercial Co-pay Program, which provides a $0 co-pay per prescription of Acthar for eligible patients with commercial or private insurance—and no government insurance.
- Information on Independent Charitable Foundations that may be able to provide funding for government-insured patients seeking financial support.
- The Acthar Patient Assistance Program, which provides Acthar at no cost for eligible uninsured, underinsured, or rendered uninsured patients.

Please see additional Important Safety Information on pages 12-14, as well as accompanying full Prescribing Information and Medication Guide.
Availability and delivery

Because Acthar is available only through what is called a Specialty Pharmacy—not your local pharmacy—the Acthar Hub coordinates the shipment of Acthar to your home or to another location as chosen by you and your child’s doctor. This process can take a few days, and it is very important that you are able to be contacted for arrangements, whether by the Specialty Pharmacy team or your child’s doctor. Please be sure to provide your child’s doctor with the best phone number to reach you, and if you miss the call from the Specialty Pharmacy, call back as soon as you can.

Around 90% of insured patients who are prescribed Acthar for IS are covered. If prior authorization paperwork is required, the Acthar Hub provides information and resources to help. You can find out more about access, reimbursement, and support at www.Acthar.com/patient.

TO LEARN MORE ABOUT THE ACTHAR HUB:
Call 1-888-435-2284
Monday through Friday, 8 AM to 9 PM ET
Saturday, 9 AM to 2 PM ET

* The Acthar Commercial Co-pay Program provides drug co-pay assistance of up to $25,000 per calendar year for each eligible patient. This program is not for patients receiving prescription reimbursement under any federal-, state-, or government-funded insurance programs or where prohibited by law. Additional Terms and Conditions and eligibility criteria apply. See terms and conditions at actharis.com/find-help-getting-acthar for full details. Mallinckrodt ARD LLC reserves the right to terminate or modify this program at any time without notice.

† Mallinckrodt does not determine Independent Charitable Foundations’ fund eligibility criteria, or have any influence over the patients or types of assistance provided.

‡ Acthar Patient Assistance Program eligibility criteria:
  • Valid Acthar prescription for an FDA-approved indication
  • Permanent US resident
  • Household income at or below 700% of the Federal Poverty Level
  • Patients may be subject to random income verification to determine eligibility

§ Program administered via a third-party organization.
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
What is the most important information I should know about Acthar? (continued)

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

- 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.
Learn about Acthar

CAREGIVER BROCHURE

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.

- 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
- 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

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

Please see additional Important Safety Information on pages 12-14, as well as accompanying full Prescribing Information and Medication Guide.

SELECT IMPORTANT SAFETY INFORMATION
TO LEARN MORE ABOUT ACTHAR, SEE HOW ACTHAR IS GIVEN, AND BROWSE AVAILABLE RESOURCES:  
Visit www.ActharIS.com

TO LEARN MORE ABOUT THE ACTHAR HUB:  
Call 1-888-435-2284  
Monday through Friday, 8 AM to 9 PM ET  
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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.

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

• 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
• 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

Please see additional Important Safety Information on pages 12-14, as well as accompanying full Prescribing Information and 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 | SUBCUTANEOUS use

Initial U.S. Approval: 1952

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; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state. (1.3 to 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 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)

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)

Decrease in Bone Density: Monitor for osteoporosis in patients on long term therapy. (5.12)

Use in Pregnancy: Embryocidal effect. Apprise women of potential harm to the fetus. (5.14)

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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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; 5 U/m² in the morning for 3 days; 2.5 U/m² in the morning for 3 days; and 1 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

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

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

5.2 Cushing’s Syndrome and Adrenal Insufficiency Upon Withdrawal
Treatment with Acthar Gel can cause hypothalamic-pituitary-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.

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, hypotension, 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
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.

5.10 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.

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 presented in Section 6.2 are primarily provided for consideration in use in adults and in children over 2 years of age treated for infantile spasms. The number of patients with infantile spasms progresses 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 angiitis (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
Exopthalmos.

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 blind) 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-cm syringe supplied with Acthar Gel, the maximum amount that can be injected is 80 U/injection, 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, dehydroepiandrosterone and a number of weakly androgenic substances. Prolonged administration of large doses of Acthar Gel induces hyperplasia and hypertrophy of the adrenal cortex and continuous high output of cortisol, corticosterone and weak androgens. The release of endogenous ACTH is under the influence of the nervous system via the regulatory hormone released from the hypothalamus and by a negative corticosteroid feedback mechanism. Elevated plasma cortisol suppresses ACTH release.

Acthar Gel is also reported to bind to melanocortin receptors.

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

Adverse 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 interpreted blind) 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. Seven of 8 patients (87.5%) responded to Acthar Gel after not responding to 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 (35° 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 (adults only) 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 live attenuated vaccines during treatment with Acthar Gel. Additionally, other immunization procedures in patients or in family members who will be in contact with the patient should be undertaken with caution while the patient is taking Acthar Gel [see Warnings and Precautions (5.4)].

Patients, their caregivers and families should be advised that the patient may experience an increase in body weight, and fecal blood loss [see Warnings and Precautions (5.5)].

Patients, their caregivers and families should be advised to monitor using coupled to actuarial costs. Patients, their caregivers and families should be advised to determine the need for use of corticosteroids during the period of stress [see Warnings and Precautions (5.2)].

Parents and caregivers should inform their physician of any change 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)].

Parents, their caregivers and families should be advised that changes in appetite, most often leading to weight gain, are seen with Acthar Gel therapy, becoming more frequent as the dose or treatment period increases. These effects are reversible once Acthar Gel therapy is stopped [see Warnings and Precautions (5.7) and Adverse Reactions (6.1.1)].

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