For severe inflammatory ophthalmic diseases

Purified Cortrophin® Gel

repository corticotropin injection USP 80 U/mL

Cortrophin Gel is an FDA-approved prescription medicine that is injected subcutaneously or intramuscularly. It is indicated for severe acute and chronic allergic and inflammatory conditions affecting the eye and its adnexa, such as[1]:

- Allergic conjunctivitis
- Keratitis
- Iritis and iridocyclitis
- Diffuse posterior uveitis and choroiditis
- Optic neuritis
- Chorioretinitis
- Anterior segment inflammation

Consider Cortrophin Gel as the next step for your patients with severe inflammatory ophthalmic diseases

Important Safety Information

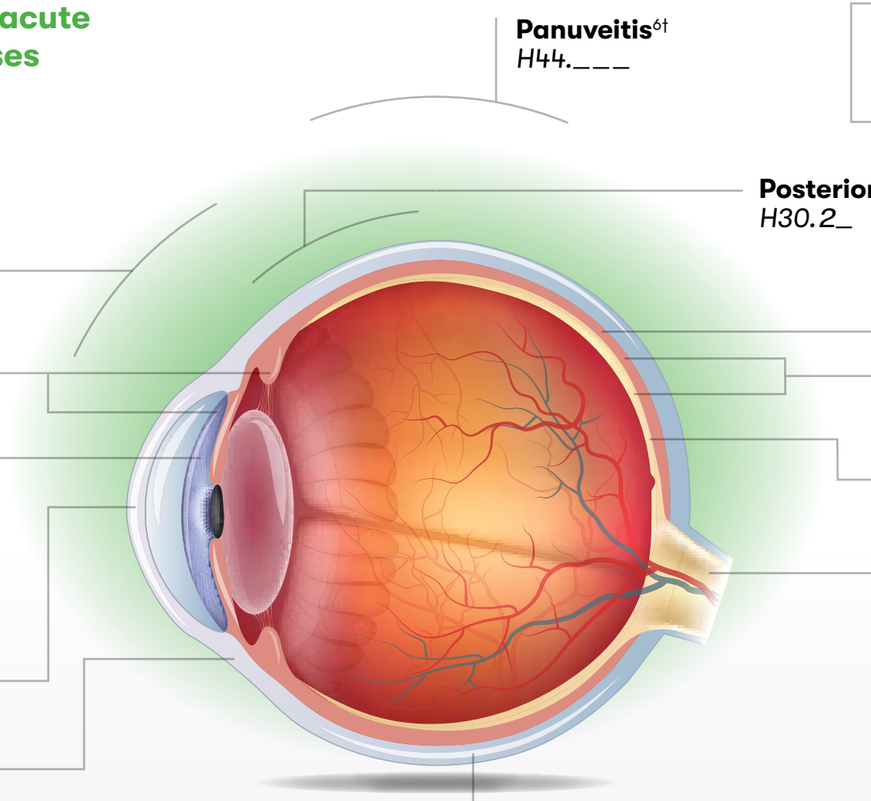
Contraindications

- Cortrophin Gel is contraindicated for intravenous administration.
- Cortrophin Gel is contraindicated in patients who have any of the following conditions: scleroderma; osteoporosis; systemic fungal infections; ocular herpes simplex; recent surgery; history of or the presence of a peptic ulcer; congestive heart failure; hypertension; primary adrenocortical insufficiency; adrenocortical hyperfunction; or sensitivity to proteins derived from porcine sources.

Please see additional Important Safety Information throughout and full Prescribing Information.

Purified Cortrophin Gel is indicated for severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:

The first 3 characters (for example, H16) of ICD-10 codes for various inflammatory conditions are presented on this page for reference. **Please refer to the next 4 pages for a complete list of ICD-10 codes.**



Other inflammatory processes involving the eye and its adnexa

- **Eyelid inflammation**[12]
  H01.___
- **Lacrimal system disorders**
  (eg, chronic dacryoadenitis)[13,14]
  H04.___
- **Orbital inflammation**[15]
  H05.___
- **Orbital myositis**[16]
  H05.___

*The anterior segment consists of the conjunctiva, cornea, anterior chamber, ciliary body, and iris.[2]
†Inflammation of all layers of the uvea (iris, ciliary body, and choroid).[5,6]

Important Safety Information (continued)

Warnings and Precautions

- **Infections:** Corticotropin therapy may increase susceptibility to infections and may mask the symptoms of infections.
- **Adrenal insufficiency:** Prolonged corticotropin therapy can increase the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by gradually reducing the corticotropin dosage. Hormone therapy should be reinstituted if stressful situations arise during discontinuation.

Please see additional Important Safety Information throughout and full Prescribing Information.

Possible relevant ICD-10 codes

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DIAGNOSIS	Right Eye	Left Eye	Bilateral	Unspecified
Other Inflammation of Eyelid				
Discoid lupus erythematosus of right upper eyelid	H01.121			
Discoid lupus erythematosus of right lower eyelid	H01.122			
Discoid lupus erythematosus of right eye, unspecified eyelid	H01.123			
Discoid lupus erythematosus of left upper eyelid		H01.124		
Discoid lupus erythematosus of left lower eyelid		H01.125		
Discoid lupus erythematosus of left eye, unspecified eyelid		H01.126		
Discoid lupus erythematosus of unspecified eye, unspecified eyelid				H01.129
Other specified inflammations of eyelid				H01.8
Unspecified inflammation of eyelid				H01.9
Disorders of Lacrimal System				
Chronic dacryoadenitis, lacrimal gland	H04.021	H04.022	H04.023	H04.029
Chronic dacryocystitis, lacrimal passage	H04.411	H04.412	H04.413	H04.419
Disorders of Orbit				
Unspecified acute inflammation of orbit				H05.00
Tenonitis	H05.041	H05.042	H05.043	H05.049
Unspecified chronic inflammatory disorders of orbit				H05.10
Granuloma	H05.111	H05.112	H05.113	H05.119
Orbital myositis	H05.121	H05.122	H05.123	H05.129
Conjunctivitis				
Acute atopic conjunctivitis	H10.11	H10.12	H10.13	
Unspecified chronic conjunctivitis	H10.401	H10.402	H10.403	H10.409

Important Safety Information (continued)

Warnings and Precautions (continued)

- **Elevated blood pressure, salt and water retention, and hypokalemia:** Corticotropin can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium or calcium.
- **Masking symptoms of other diseases:** Corticotropin may only suppress signs and symptoms of chronic disease without altering the natural course of disease.

Possible relevant ICD-10 codes (continued)

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DIAGNOSIS	Right Eye	Left Eye	Bilateral	Unspecified
Conjunctivitis (cont.)				
Chronic giant papillary conjunctivitis	H10.411	H10.412	H10.413	H10.419
Simple chronic conjunctivitis	H10.421	H10.422	H10.423	H10.429
Chronic follicular conjunctivitis	H10.431	H10.432	H10.433	H10.439
Vernal conjunctivitis				H10.44
Other chronic allergic conjunctivitis				H10.45
Ligneous conjunctivitis	H10.511	H10.512	H10.513	H10.519
Disorders of Sclera				
Unspecified scleritis	H15.001	H15.002	H15.003	H15.009
Anterior scleritis	H15.011	H15.012	H15.013	H15.019
Posterior scleritis	H15.031	H15.032	H15.033	H15.039
Scleritis with corneal involvement	H15.041	H15.042	H15.043	H15.049
Other scleritis	H15.091	H15.092	H15.093	H15.099
Keratitis				
Unspecified corneal ulcer	H16.001	H16.002	H16.003	H16.009
Central corneal ulcer	H16.011	H16.012	H16.013	H16.019
Ring corneal ulcer	H16.021	H16.022	H16.023	H16.029
Corneal ulcer with hypopyon	H16.031	H16.032	H16.033	H16.039
Marginal corneal ulcer	H16.041	H16.042	H16.043	H16.049
Mooren's corneal ulcer	H16.051	H16.052	H16.053	H16.059
Perforated corneal ulcer	H16.071	H16.072	H16.073	H16.079
Unspecified superficial keratitis	H16.101	H16.102	H16.103	H16.109
Macular keratitis	H16.111	H16.112	H16.113	H16.119
Filamentary keratitis	H16.121	H16.122	H16.123	H16.129
Punctate keratitis	H16.141	H16.142	H16.143	H16.149

Important Safety Information (continued)

Warnings and Precautions (continued)

- **Psychiatric reactions:** Psychic derangements may appear when corticotropin is used, ranging from euphoria, insomnia, mood swings, personality changes, and depression to psychosis. Existing conditions may be aggravated.
- **Ophthalmic reactions:** Prolonged use of corticotropin may produce posterior subcapsular cataracts and glaucoma with possible damage to the optic nerves.

Possible relevant ICD-10 codes (continued)

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DIAGNOSIS	Right Eye	Left Eye	Bilateral	Unspecified
Keratitis (continued)				
Unspecified keratoconjunctivitis	H16.201	H16.202	H16.203	H16.209
Keratoconjunctivitis sicca, not specified as Sjögren's	H16.221	H16.222	H16.223	H16.229
Vernal keratoconjunctivitis, with limbar and corneal involvement	H16.261	H16.262	H16.263	H16.269
Other keratoconjunctivitis	H16.291	H16.292	H16.293	H16.299
Unspecified interstitial keratitis	H16.301	H16.302	H16.303	H16.309
Diffuse interstitial keratitis	H16.321	H16.322	H16.323	H16.329
Sclerosing keratitis	H16.331	H16.332	H16.333	H16.339
Other interstitial and deep keratitis	H16.391	H16.392	H16.393	H16.399
Other keratitis				H16.8
Unspecified keratitis				H16.9
Iridocyclitis				
Unspecified acute and subacute iridocyclitis				H20.00
Primary iridocyclitis	H20.011	H20.012	H20.013	H20.019
Recurrent acute iridocyclitis	H20.021	H20.022	H20.023	H20.029
Secondary noninfectious iridocyclitis	H20.041	H20.042	H20.043	H20.049
Hypopyon	H20.051	H20.052	H20.053	H20.059
Chronic iridocyclitis	H20.11	H20.12	H20.13	H20.10
Vogt-Koyanagi syndrome	H20.821	H20.822	H20.823	H20.829
Unspecified iridocyclitis				H20.9
Chorioretinal Inflammation				
Unspecified focal chorioretinal inflammation	H30.001	H30.002	H30.003	H30.009
Focal chorioretinal inflammation, juxtapapillary	H30.011	H30.012	H30.013	H30.019
Focal chorioretinal inflammation of posterior pole	H30.021	H30.022	H30.023	H30.029
Focal chorioretinal inflammation, peripheral	H30.031	H30.032	H30.033	H30.039
Focal chorioretinal inflammation, macular or paramacular	H30.041	H30.042	H30.043	H30.049

Important Safety Information (continued)

Warnings and Precautions (continued)

- **Immunogenicity potential:** Prolonged administration of Cortrophin Gel may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH and Cortrophin Gel activity.

Possible relevant ICD-10 codes (continued)

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DIAGNOSIS	Right Eye	Left Eye	Bilateral	Unspecified
Chorioretinal Inflammation (continued)				
Unspecified disseminated chorioretinal inflammation	H30.101	H30.102	H30.103	H30.109
Disseminated chorioretinal inflammation of posterior pole	H30.111	H30.112	H30.113	H30.119
Disseminated chorioretinal inflammation, peripheral	H30.121	H30.122	H30.123	H30.129
Disseminated chorioretinal inflammation, generalized	H30.131	H30.132	H30.133	H30.139
Acute posterior multifocal placoid pigment epitheliopathy	H30.141	H30.142	H30.143	H30.149
Posterior cyclitis	H30.21	H30.22	H30.23	H30.20
Harada's disease	H30.811	H30.812	H30.813	H30.819
Other chorioretinal inflammations	H30.891	H30.892	H30.893	H30.899
Unspecified chorioretinal inflammation	H30.91	H30.92	H30.93	H30.90
Other Retinal Disorders				
Retinal vasculitis	H35.061	H35.062	H35.063	H35.069
Disorders of Globe				
Panuveitis	H44.111	H44.112	H44.113	H44.119
Sympathetic uveitis	H44.131	H44.132	H44.133	H44.139
Optic Neuritis				
Optic papillitis	H46.01	H46.02	H46.03	H46.00
Retrobulbar neuritis	H46.11	H46.12	H46.13	H46.10
Other optic neuritis				H46.8
Unspecified optic neuritis				H46.9
Other Disorders of Optic [2nd] Nerve and Visual Pathways				
Ischemic optic neuropathy	H47.011	H47.012	H47.013	H47.019
Pemphigoid				
Cicatricial pemphigoid				L12.1

Important Safety Information (continued)

Warnings and Precautions (continued)

- **Vaccination:** Patients should not be vaccinated against smallpox while on corticotropin therapy. Other immunizations should be undertaken with caution due to possible neurologic complications and lack of antibody response.

Which of your patients may be appropriate for Cortrophin Gel?

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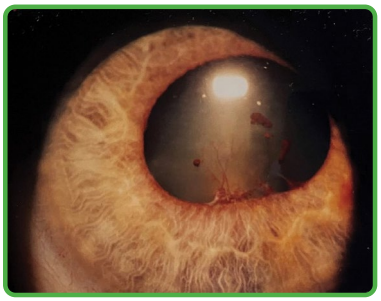
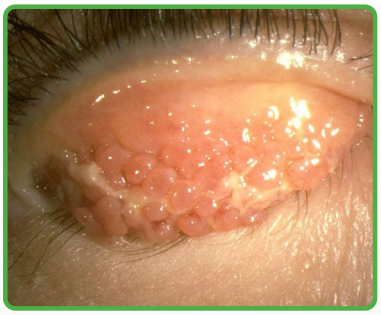
Cortrophin Gel is a prescription medicine that is injected subcutaneously or intramuscularly. It is indicated for severe acute and chronic allergic and inflammatory conditions affecting the eye and its adnexa, such as allergic conjunctivitis, keratitis, iritis and iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.



Iritis[17]*

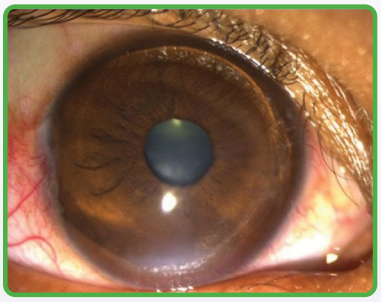
Signs and symptoms include redness, pain, blurred vision, light sensitivity, anterior and posterior synechiae, pupillary changes, and floaters.[18,19]



Keratoconjunctivitis[20]†

Signs and symptoms include bilateral inflammation of the conjunctiva and sclera, characterized by intense itching, photophobia, and redness. This often manifests as cobblestone-like papillae on the upper palpebral conjunctiva, along with discharge. Patients may also develop gelatinous nodules adjacent to the cornea (limbus), corneal scarring (shield ulcers), or cataract formation, potentially leading to blurred vision or reduced visual acuity.[21]

Image shows giant papillae in vernal keratoconjunctivitis.



Keratitis[22]‡

Signs and symptoms include severe eye pain, redness, and blurred vision. Patients often experience sensitivity to light, tearing, and a feeling of something in the eye. Clinical signs may also include a visible ulcer on the cornea, along with pus or other discharge.[23]

*Image courtesy of Maria Sieglinda von Nudeldorf, Creative Commons BY-SA 4.0, via Wikimedia Commons.
†Image courtesy of Tony Ching, EyeWiki, American Academy of Ophthalmology.
‡Originally published by and used with permission from Dove Medical Press Ltd.

Important Safety Information (continued)

Warnings and Precautions (continued)

- **Use in patients with hypothyroidism and cirrhosis:** There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis.
- **Use in patients with latent tuberculosis or tuberculin reactivity:** Closely observe for reactivation of the disease.

Which of your patients may be appropriate for Cortrophin Gel? (continued)

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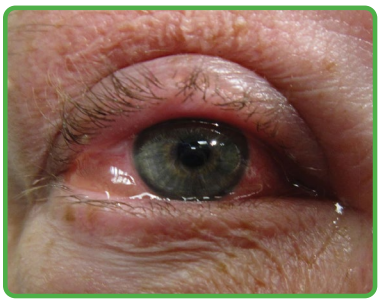
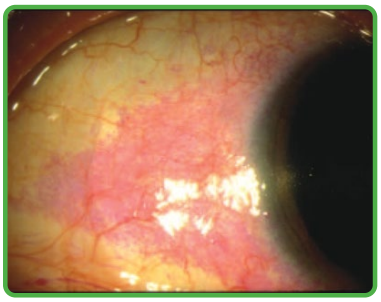


Allergic conjunctivitis[24§]

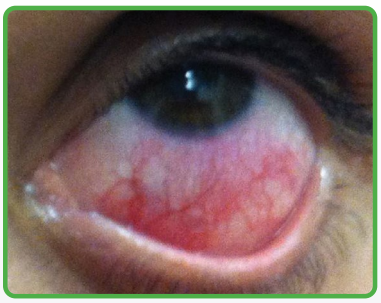
Signs and symptoms include itching and edematous, diffusely hyperemic eyelids and conjunctiva. Patients commonly present with bilateral conjunctival injection, chemosis, and both watery and mild mucous discharge.[25]



Dry eye disease (keratoconjunctivitis sicca)[26¶]

Signs and symptoms include tearing, burning, stinging, itching, a scratchy or foreign-body sensation, discharge, frequent blinking, mattering or caking of the eyelashes (usually worse upon waking), redness, blurry or fluctuating vision (made worse when reading, using a computer, watching television, and driving), light-sensitivity, eye pain, and eye fatigue.[27]

Image shows staining of the conjunctiva with rose bengal.



Scleritis[28#]

Signs and symptoms include painful, red eyes and inflammation of the sclera (with or without vision loss). Scleritis presents with a characteristic violet-bluish hue with scleral edema and dilatation.[29]

§Image courtesy of James Heilman, MD, Creative Commons BY 4.0, via Wikimedia Commons.
¶Image courtesy of the American Academy of Ophthalmology.
#Image courtesy of Marc Yonkers, MD, Phd. *Western Journal of Emergency Medicine.*

For your DIFFICULT-TO-TREAT patients, consider Cortrophin Gel as a potential next step in their treatment journey

Important Safety Information (continued)

Warnings and Precautions (continued)

- **Comorbid diseases:** Corticotropin should be used with caution in patients with diabetes, abscess, pyogenic infections, diverticulitis, renal insufficiency, and myasthenia gravis.
- **Growth and development:** Carefully observe growth and development of infants and children on prolonged corticotropin therapy.

Proposed mechanism of action of ACTH

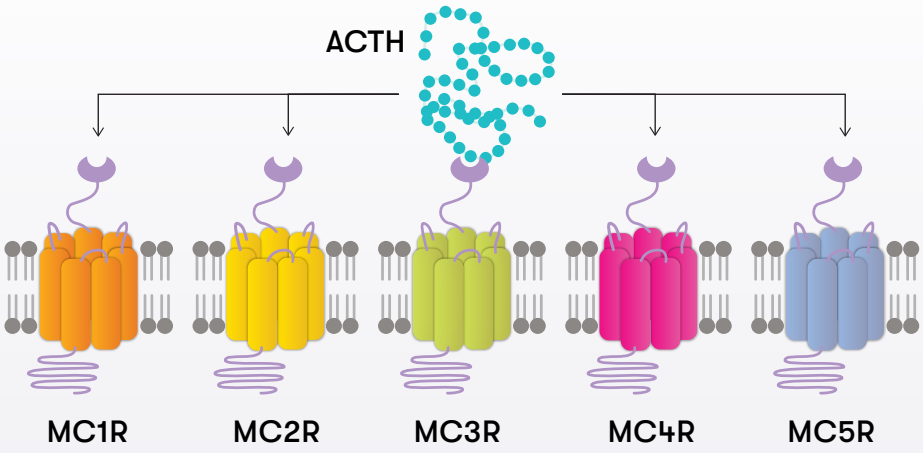
Purified Cortrophin® Gel (repository corticotropin injection USP) is a naturally sourced, purified corticotropin (ACTH) that is made up of a complex mixture of ACTH, ACTH-related peptides, and other natural pituitary-derived peptides.[1] The exact mechanism of action of Cortrophin Gel is unknown and requires further investigation. The following information is based on nonclinical and pharmacodynamic data, and the relationship to clinical benefit is unknown.

ACTH may work through the melanocortin pathway.[30]

Melanocortin receptors are receptors on immune and other cells throughout the body that may play a role in regulating the immune response.[31-33] Preclinical data suggest leveraging the melanocortin signaling pathway may represent an important therapeutic strategy.[31-33]

ACTH may possess both steroid-dependent and steroid-independent activity

Steroidogenic	Steroid-independent
In vitro, ACTH binds to melanocortin receptor 2 (MC2R) on the adrenal cortex, causing release of cortisol[30,34]	In vitro, ACTH binds to all 5 MCRs, which may affect pathways distinct from the steroidogenic pathway[30,35-37]



ACTH=adrenocorticotropic hormone; α-MSH=alpha-melanocyte stimulating hormone; MCR=melanocortin receptor.

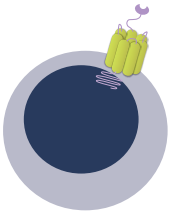
Important Safety Information (continued)

Warnings and Precautions (continued)

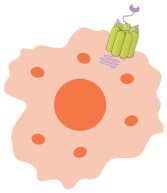
- **Acute gouty arthritis:** Treatment of acute gouty arthritis should be limited to a few days. Conventional concomitant therapy should be administered during corticotropin treatment and for several days after it is stopped.

Proposed mechanism of action of ACTH (continued)

Preclinical human and animal studies using ACTH, and its truncated analog, α-MSH, suggest ACTH binds to various immune cells

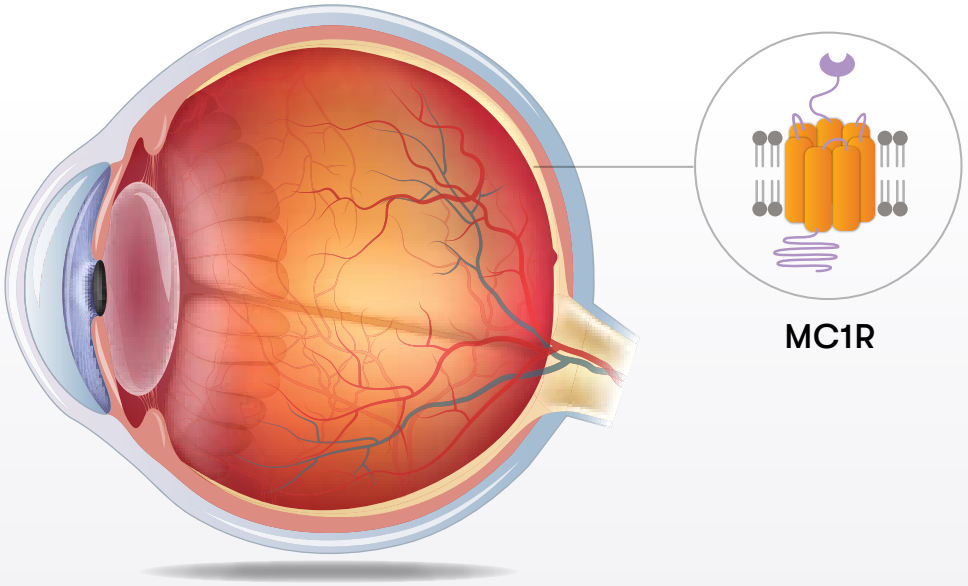


Human $CD4^+$ T cells have been shown to express MC1R, MC2R, MC3R, and MC5R[38,39]



Human macrophages have been shown to express MC1R, MC3R, and MC5R[40,41]

A preclinical study using α-MSH, a truncated ACTH analog, suggests that MC1R is expressed in the human retina



MC1R expression has been shown in human retinal pigment epithelium (RPE) cells[42]

Important Safety Information (continued)

Warnings and Precautions (continued)

- **Drug interactions:** Aspirin should be used cautiously with corticotropin in hypoprothrombinemia.
- **Pregnancy:** Since fetal abnormalities have been observed in animals, Cortrophin Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

For severe inflammatory ophthalmic diseases

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Is Cortrophin Gel the appropriate next step for your patient?

Important Safety Information (continued)

Adverse Reactions
Adverse reactions for Cortrophin Gel include fluid or sodium retention; muscle weakness; osteoporosis; peptic ulcer with possible perforation and hemorrhage; injection site reactions; impaired wound healing; hypertension; convulsions; headache; development of Cushingoid state; suppression of growth in children; and weight gain. These are not all the adverse reactions reported with Cortrophin Gel.

Please see additional Important Safety Information throughout and full Prescribing Information.

Learn more about prescribing Cortrophin Gel by visiting Cortrophin.com/prescribe or by scanning this QR code

References: 1. Purified Cortrophin Gel. Package insert. ANI Pharmaceuticals, Inc. **2.** Akhter MH et al. *Gels.* 2022;8(2):82. **3.** Maring M, et al. *Ocul Immunol Inflamm.* 2022;30(2):357-363. **4.** Harthan JS et al. *Clin Optom* 2016;8:23-35. **5.** Bielory L. *J Allergy Clin Immunol.* 2000;106(5):805-816. **6.** Jabs DA et al. *Am J Ophthalmol.* 2005;140(3):509-516. **7.** Sacchetti M, et al. *Life (Basel).* 2021;11(10):1012. **8.** Koganti R, et al. *Exp Eye Res.* 2021;205:108483. **9.** Walton RC, Ashmore ED. *Curr Opin Ophthalmol.* 2003;14(6):413-419. **10.** Shen Lee B, et al. *Ophthalmol Ther.* 2022;11(4):1333-1369. **11.** Rolando M, Barabino S. *Int J Mol Sci.* 2023;24(2):1458. **12.** Bernardes TF, Bonfioli AA. *Semin Ophthalmol.* 2010;25(3):79-83. **13.** Zoukhri D. *Exp Eye Res.* 2006;82(5):885-898. **14.** Sundar G, et al. American Academy of Ophthalmology. EyeWiki. Accessed July 17, 2024. https://eyewiki.aao.org/Dacryoadenitis **15.** Lutt JR et al. *Semin Arthritis Rheum.* 2008;37(4):207-222. **16.** Brent H, Sidlow R. *Clin Pediatr (Phila).* 2017;56(4):385-388. **17.** Wikimedia Commons. Accessed July 17, 2024. https://commons.wikimedia.org/wiki/File:Vascularised_posterior_synechia.jpg **18.** Rosenbaum JT, et al. *Semin Arthritis Rheum.* 2019;49(3):438-445. **19.** Feldman B, et al. American Academy of Ophthalmology. EyeWiki. Accessed July 24, 2024. https://eyewiki.org/Acute_Anterior_Uveitis **20.** Ching, T. Vernal Keratoconjunctivitis. American Academy of Ophthalmology. EyeWiki. Accessed September 3, 2024. https://eyewiki.org/File:AA0_4068.jpg **21.** Vernal Keratoconjunctivitis. National Organization for Rare Disorders. Updated April 4, 2022. Accessed August 28, 2024. https://rarediseases.org/rare-diseases/vernal-keratonconjunctivitis/ **22.** Sabhapandit S, et al. *Clin Optom.* 2022; Volume 16:3547-355. **23.** What Is a Corneal Ulcer (Keratitis)? American Academy of Ophthalmology. Updated November 21, 2023. Accessed September 3, 2024. https://www.aao.org/eye-health/diseases/corneal-ulcer **24.** Wikimedia Commons. Accessed July 17, 2024. https://commons.wikimedia.org/wiki/File:Allergicconjunctivitis.jpg **25.** Adamopoulou C, et al. American Academy of Ophthalmology. EyeWiki. Accessed July 24, 2024. https://eyewiki.aao.org/Allergic_Conjunctivitis **26.** Milner MS, et al. *Curr Opin Ophthalmol.* 2017;28:3-47. **27.** Patel A, et al. American Academy of Ophthalmology. EyeWiki. Accessed July 24, 2024. https://eyewiki.aao.org/Dry_Eye_Syndrome **28.** Gilani CJ et al. *West J Emerg Med.* 2017;18(3):509-517. **29.** Feldman B, et al. American Academy of Ophthalmology. EyeWiki. Accessed July 24, 2024. https://eyewiki.aao.org/Scleritis **30.** Mountjoy KG, et al. *Science.* 1992;257(5074):1248-1251. **31.** Zhong Q, et al. *Bone.* 2005;36(5):820-831. **32.** Lindskog A, et al. *J Am Soc Nephrol.* 2010;21(8):1290-1298. **33.** Delgado R, et al. *J Leukoc Biol.* 1998;63(6):740-745. **34.** Montero-Melendez T. *Semin Immunol.* 2015;27(3):216-226. **35.** Gantz I, et al. *J Biol Chem.* 1993;268(11):8246-8250. **36.** Gantz I, et al. *J Biol Chem.* 1993;268(20):15174-15179. **37.** Chhajlani V, et al. *Biochem Biophys Res Commun.* 1993;195:866-873. **38.** Andersen GN, et al. *Scand J Immunol.* 2005;61(3):279-284. **39.** Zhao J, et al. *JCI Insight.* 2021;6(13):e143385. **40.** Yoon SW, et al. *J Biol Chem.* 2003;278(35):32914-32920. **41.** ATCC. THP-1. Accessed December 7, 2023. https://www.atcc.org/products/tib-202 **42.** Cheng L, et al. *Biochem Biophys Res Commun.* 2014;443(2):447-452.

ani Pharmaceuticals, Inc.

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