CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

008975Orig1s008

Trade Name:	PURIFIED CORTROPHIN GEL
Generic or Proper Name:	(repository corticotropin injection USP)
Sponsor:	ANI Pharmaceuticals, Inc.
Approval Date:	October 29, 2021
Indication:	Purified Cortrophin Gel is indicated in the following disorders: 1. Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis. Reference ID: 4880561 Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). Ankylosing spondylitis. Acute gouty arthritis. 2. Collagen diseases: During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus. Systemic dermatomyositis (polymyositis). 3. Dermatologic diseases: Severe erythema multiforme (Stevens-Johnson syndrome).

Severe psoriasis.
4. Allergic states:
Atopic dermatitis.
Serum sickness.
5. Ophthalmic diseases:
Severe acute and chronic allergic and inflammatory processes involving the eye and its
adnexa such as:
Allergic conjunctivitis.
Keratitis.
Iritis and iridocyclitis.
Diffuse posterior uveitis and choroiditis.
Optic neuritis.
Chorioretinitis.
Anterior segment inflammation.
6. Respiratory diseases:
Symptomatic sarcoidosis.
7. Edematous states:
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.
8. Nervous system:
Acute exacerbations of multiple sclerosis.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

008975Orig1s008

APPROVAL LETTER

NDA 008975/S-008

SUPPLEMENT APPROVAL

ANI Pharmaceuticals, Inc.
Attention: Ellen Connolly
Vice President, Regulatory Affairs
210 Main Street West
Baudette, MN 56623

Dear Ms. Connolly:

Please refer to your supplemental new drug application (sNDA) dated June 29, 2021, received June 29, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for purified Cortrophin Gel (repository corticotrophin injection USP).

This Prior Approval sNDA provides for quality information and supporting data for reintroduction of the product in the US market.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible from publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling (carton labeling submitted on June 29, 2021, and container labeling submitted on August 17, 2021), as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labeling for approved NDA 008975/S-008**." Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information aabout submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format – Promotional Labeling and Advertisign in Materials for Human Prescription Drugs*.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call Dana Smith, Regulatory Project Manager, at 240-402-9906.

Sincerely,

{See appended electronic signature page}

Naomi Lowy, MD
Deputy Director
Division of General Endocrinology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Instructions for Use
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAOMI N LOWY
10/29/2021 08:52:24 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

008975Orig1s008

OTHER ACTION LETTERS

NDA 008975/S-008

REFUSAL TO FILE

ANI Pharmaceuticals, Inc.
Attention: Kassidy Good
Director Corticotropin Regulatory Affairs
210 Main Street West
Baudette, MN 56623

Dear Ms. Good:

Please refer to your supplemental new drug application (NDA), received March 23, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for purified Cortrophin Gel (repository corticotrophin injection USP).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Chemistry, Manufacturing and Controls

1. Immunogenicity

In our General Advice Letter, dated May 18, 2018, and our response to questions in your meeting package, dated March 15, 2018, you were advised that your proposed product may have differences (b) (4) compared to the previously marketed product that may affect safety of your product – notably immunogenicity. In your response you stated, "The most important addition made (b) (4) from the last approved product is (b) (4) You further suggested in your response that your proposed product and the approved product were similar "with no added concern that would increase immunogenicity beyond what is currently on the label." We do not consider your response as adequate to address the potential concern for immunogenicity.

Conduct a risk assessment to address patient or product specific factors that can affect immunogenicity particularly with the multiple indications as proposed in your package insert.

2. Virus clearance/validation

You provided study reports for virus clearance/validation from the contract laboratory (b) (4) but it is not possible to review those reports because details on the preparation of samples for viral clearance are not disclosed. (b) (4)

(b) (4)

(b) (4)
. Submit a virus clearance/validation study report taking the above suggestions into consideration.

We also encourage you to consider redesigning a fit-for-purpose virus clearance/validation study appropriate to your manufacturing process with a well-developed scaled-down model. In addition to model viruses studied, you might consider including a model retrovirus in the virus clearance study (to serve as a model for porcine endogenous retroviruses, which have been shown to be infectious, unlike endogenous retroviruses from other species[2,3]).

You may also consider possible improvements to your manufacturing process (b) (4) (b) (4) to improve the potential for viral clearance.

3. Drug Substance Manufacturing

(b) (4)

(b) (4)

[2] Infection of human cells by an endogenous retrovirus of pigs, C. Patience et al., Nature Medicine, 3, 282-286 (1997).

[3] The porcine virome and xenotransplantation, J. Denner, Virology Journal, 14, 171-177 (2017).

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

(b) (4)

4. Microbiology

Your supplemental NDA lacks essential microbiological information that precludes a review to assess the sterility assurance for your product.

- The following validation reports were not provided: container closure integrity test (CCIT), (b) (4) validation, vial depyrogenation process, (b) (4) (b) (4).
- The description of the proposed manufacturing area and the facility floor plan/layouts were not provided.
- The Water For Injection monitoring and environmental monitoring program were not described.
- The (b) (4) bioburden specification (b) (4) (b) (4) were not provided.
- The actions to be taken in event of a (b) (4) failure were not described.
- It is noted that Antimicrobial Effectiveness Test (AET) will be conducted (b) (4) (b) (4) for one submission batch. It is further noted that the drug product package insert does not indicate an after opening expiry and that the vial will be warmed up prior to use and returned to 2-8°C conditions after each use. A risk assessment summarizing studies that demonstrate preservative efficacy under the specified in-use storage conditions (i.e., store at 2-8°C and warm up prior to each use) was not provided.

For more information please refer to the Agency's 1994 Guidance for Industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (b) (4).

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, call Dana Smith, Regulatory Project Manager, at 1-240-402-9906.

Sincerely yours,

{See appended electronic signature page}

Theresa E. Kehoe, MD
Division Director (Acting)
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA E KEHOE
04/27/2020 03:53:30 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

008975Orig1s008

LABELING

PURIFIED CORTROPHIN® GEL
(Repository Corticotropin Injection USP)

Rx only

DESCRIPTION

Purified Cortrophin Gel is a porcine derived purified corticotropin (ACTH) in a sterile solution of gelatin. It is made up of a complex mixture of ACTH, ACTH related peptides and other porcine pituitary derived peptides.

The drug product is a sterile preparation containing 80 USP units per mL and it contains 0.5% phenol (as preservative), 15.0% gelatin (for prolonged activity), water for injection, and the pH is adjusted with hydrochloric acid and sodium hydroxide.

Purified Cortrophin Gel contains the porcine derived ACTH (1-39) with the following amino acid sequence:

Ser- 1	Tyr- 2	Ser- 3	Met- 4	Glu- 5	His- 6	Phe- 7	Arg- 8	Trp- 9	Gly- 10
Lys- 11	Pro- 12	Val- 13	Gly- 14	Lys- 15	Lys- 16	Arg- 17	Arg- 18	Pro- 19	Val- 20
Lys- 21	Val- 22	Tyr- 23	Pro- 24	Asn- 25	Gly- 26	Ala- 27	Glu- 28	Asp- 29	Glu- 30
Leu- 31	Ala- 32	Glu- 33	Ala- 34	Phe- 35	Pro- 36	Leu- 37	Glu- 38	Phe- 39	OH

CLINICAL PHARMACOLOGY

Purified Cortrophin Gel is the anterior pituitary hormone which stimulates the functioning adrenal cortex to produce and secrete adrenocortical hormones.

Following administration of a single intramuscular injection of 80 Units of Cortrophin gel to healthy volunteers (n=20) in an open label pharmacodynamic study, the median time (range) to reach peak cortisol concentration was 8 (3-12) hours. The baseline corrected geometric mean maximum (CV%) cortisol levels were 34.52 µg/dL (28.2%).

INDICATIONS AND USAGE

Purified Cortrophin Gel is indicated in the following disorders:

1. 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.
Acute gouty arthritis.

2. Collagen diseases:
   During an exacerbation or as maintenance therapy in selected cases of:
   Systemic lupus erythematosus.
   Systemic dermatomyositis (polymyositis).
3. Dermatologic diseases:
   Severe erythema multiforme (Stevens-Johnson syndrome).
   Severe psoriasis.
4. Allergic states:
   Atopic dermatitis.
   Serum sickness.
5. Ophthalmic diseases:
   Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
   Allergic conjunctivitis.
   Keratitis.
   Iritis and iridocyclitis.
   Diffuse posterior uveitis and choroiditis.
   Optic neuritis.
   Chorioretinitis.
   Anterior segment inflammation.
6. Respiratory diseases:
   Symptomatic sarcoidosis.
7. Edematous states:
   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.
8. Nervous system:
   Acute exacerbations of multiple sclerosis.

CONTRAINDICATIONS

Purified Cortrophin Gel is contraindicated for intravenous administration.

Purified Cortrophin 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, hypertension, or sensitivity to proteins derived from porcine sources.

Purified Cortrophin Gel is contraindicated in patients with primary adrenocortical insufficiency or adrenocortical hyperfunction.

WARNINGS

Chronic administration of corticotropin may lead to adverse effects which are not reversible.

This product should not be administered for treatment until adrenal responsiveness has been verified with the route of administration which will be utilized during treatment, intramuscularly or subcutaneously. A rise in urinary and plasma corticosteroid values provides direct evidence of a stimulatory effect. Although the action of corticotropin is similar to that of exogenous adrenocortical steroids the quantity of adrenocorticoid may be variable. In patients who receive prolonged corticotropin therapy the additional use of rapidly acting corticosteroids before, during and after an unusual stressful situation is indicated.

Masking Symptoms of Other Diseases

Corticotropin may only suppress symptoms and signs of chronic disease without altering the natural course of the disease.

Immunogenicity Potential

Purified Cortrophin Gel is immunogenic. Limited available data suggest that a patient may develop antibodies to Purified Cortrophin Gel after chronic administration and loss of endogenous ACTH and Purified Cortrophin Gel activity. Prolonged administration of Purified Cortrophin 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.

Ophthalmic Effects

Prolonged use of corticotropin may produce posterior subcapsular cataracts and glaucoma with possible damage to the optic nerves.

Infections

Corticotropin may mask some signs of infection, and new infections including those of the eye due to fungi or viruses may appear during its use. There may be decreased resistance and inability to localize infection when corticotropin is used.

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. Dietary salt restriction and potassium supplementation may be necessary. Corticotropin increases calcium excretion.

Vaccination

While on corticotropin therapy, patients should not be vaccinated against smallpox. Other immunization procedures should be undertaken with caution in patients who are receiving corticotropin, especially when high doses are administered because of the possible hazards of neurological complications and lack of antibody response.

PRECAUTIONS

General

Patients with latent tuberculosis or tuberculin reactivity who receive corticotropin should be closely observed as reactivation of the disease may occur. During prolonged corticotropin therapy, these patients should receive chemoprophylaxis.

Skin testing should be performed prior to treatment of all patients with suspected sensitivity to porcine protein. Immediately following intramuscular or subcutaneous administration of corticotropin all patients should be observed carefully for sensitivity reactions.

Relative adrenocortical insufficiency induced by prolonged corticotropin therapy may be minimized by gradual reduction of corticotropin dosage. This type of insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress during that period, hormone therapy should be reinstituted.

There is an enhanced effect of corticotropin in patients with hypothyroidism and in those with cirrhosis.

The lowest possible dosage of corticotropin should be used to control the condition under treatment, and when reduction in dosage is possible the reduction should be gradual.

Corticotropin should be administered for treatment only when the disease is intractable to more conventional therapy. Corticotropin should be adjunctive and not the sole therapy in the treatment of a disease.

Since maximal corticotropin stimulation of the adrenals may be limited during the first few days of treatment, other drugs should be administered when an immediate therapeutic effect is desirable.

When infection is present appropriate anti-infective therapy should be administered during corticotropin and following discontinuation of corticotropin therapy.

Treatment of acute gouty arthritis should be limited to a few days. Since rebound attacks may occur when corticotropin is discontinued, conventional concomitant therapy should be administered during corticotropin treatment, and for several days after it is stopped.

Psychic derangements may appear when corticotropin is used, ranging from euphoria, insomnia, mood swings, personality changes, and depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticotropin.

Corticotropin should be used with caution in patients with diabetes, abscess, pyogenic infections, diverticulitis, renal insufficiency, and myasthenia gravis.

Growth and development of infants and children on prolonged corticotropin therapy should be carefully observed.

Although controlled clinical trials have shown ACTH to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that it affects the ultimate outcome or natural history of the disease.

Since complications of treatment with ACTH are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment.

Drug Interactions

Aspirin should be used cautiously in conjunction with corticotropin in hypoprothrombinemia.

Pregnancy

Since fetal abnormalities have been observed in experimental animals, use of this drug in pregnancy, nursing mothers, or women of childbearing potential requires that the potential benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticotropin during pregnancy should be carefully observed for signs of hypoadrenalism.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances
Sodium retention.
Hypokalemic alkalosis.
Fluid retention.
Calcium loss.
Potassium loss.

Musculoskeletal
Muscle weakness.
Loss of muscle mass.
Steroid myopathy.
Osteoporosis.
Vertebral compression fractures.
Aseptic necrosis of femoral and humeral heads.
Pathologic fracture of long bones.

Gastrointestinal
Peptic ulcer with possible perforation and hemorrhage.
Abdominal distention.
Ulcerative esophagitis.
Pancreatitis.

Dermatologic
Impaired wound healing.
Increased sweating.
Thin fragile skin.

Suppression of skin test reactions.
Petechiae and ecchymoses.
Acne.
Hyperpigmentation.
Facial erythema.

Cardiovascular
Hypertension.
Congestive heart failure.
Necrotizing angiitis.

Neurological
Convulsions.
Increased intracranial pressure with papilledema (pseudo-tumor cerebri), usually after treatment.
Headache.
Vertigo.

Endocrine
Menstrual irregularities.
Development of Cushingoid state.
Suppression of growth in children.
Secondary adrenocortical and pituitary insufficiency, particularly in times of stress, as in trauma, surgery or illness.
Decreased carbohydrate tolerance.
Manifestations of latent diabetes mellitus.
Increased requirements for insulin or oral hypoglycemic agents in diabetics.
Hirsutism.

Ophthalmic
Posterior subcapsular cataracts.
Increased intraocular pressure.
Glaucoma with possible damage to optic nerve.
Exophthalmos.

Metabolic
Negative nitrogen balance due to protein catabolism.

Allergic reactions
Allergic reactions manifesting as dizziness, nausea and vomiting, shock, skin reactions, especially in patients with allergic responses to proteins.

Miscellaneous
Abscess.
Development of antibodies and loss of stimulatory effect.

To report SUSPECTED ADVERSE REACTIONS, contact ANI Pharmaceuticals, Inc. at 1-800-308-6755 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION

Standard tests for verification of adrenal responsiveness to corticotropin may utilize as much as 80 units as a single injection or one or more injections of a lesser dosage. Verification tests should be performed prior to treatment with corticotropins. The test should utilize the route(s) of administration proposed for treatment. Following verification 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, plasma and urine corticosteroid levels and the initial response of the patient. Only gradual change in dosage schedules should be attempted, after full drug effects have become apparent.

In the treatment of acute exacerbations of multiple sclerosis daily intramuscular doses of 80-120 units for 2-3 weeks.

The chronic administration of more than 40 units daily may be associated with uncontrollable adverse effects.

When reduction in dosage is indicated this should be accomplished gradually by either reducing the amount of each injection, or administering injections at longer intervals, or by a combination of both of the above. During reduction of dosage, careful consideration should be given to the disease being treated, the general medical condition of the patient and the duration over which corticotropin was administered.

This product may be administered subcutaneously or intramuscularly.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED/STORAGE AND HANDLING

Purified Cortrophin Gel is supplied sterile in 5 mL multiple-dose vials (NDC 62559-860-15) containing 80 USP units/mL.

Store Purified Cortrophin Gel refrigerated at 2° to 8°C (36° to 46°F).

Distributed by:
ANI Pharmaceuticals, Inc.
Baudette, MN 56623

10233 Rev 10/21

INSTRUCTIONS FOR USE
Purified Cortrophin® Gel
(Repository Corticotropin Injection USP)
for intramuscular or subcutaneous use

This Instructions for Use contains information on how to inject Purified Cortrophin Gel.

Your healthcare provider should show you how to prepare and inject Purified Cortrophin Gel the right way before you inject it for the first time. Do not try to inject yourself until you have been shown the right way to give your injections by your healthcare provider.

Important information about how to inject Purified Cortrophin Gel
Purified Cortrophin Gel is given as an injection into the muscle or under the skin as directed by your healthcare provider. Do not inject it into a vein or take by mouth.

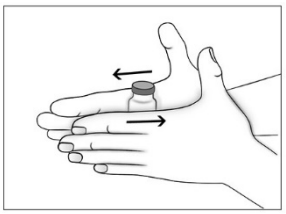
- Inject Purified Cortrophin Gel exactly as your healthcare provider tells you. Your healthcare provider will tell you where to give the injection, how much to give, how often and when to give it.
- Do not use Purified Cortrophin Gel until your healthcare provider has taught you how to give the injection.

Before starting, collect all of the supplies that you will need to use for preparing and injecting Purified Cortrophin Gel. You will need the following supplies:

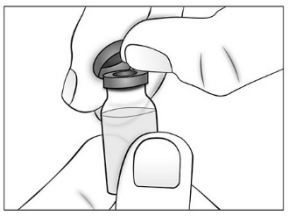
- Vial of Purified Cortrophin Gel
- Syringe
- Needle for withdrawal (20G or as prescribed by your healthcare provider)
- Needle for injection (23G or as prescribed by your healthcare provider)
- Several alcohol pads
- Cotton balls or gauze pad
- Bandage (if needed)
- Sharps container for throwing away used syringes and needles.

Preparing Purified Cortrophin Gel

- Wash your hands thoroughly and dry with a clean towel.
- Remove the vial from the refrigerator. Check the expiration date on the vial; do not use if the expiration date has passed.
- Purified Cortrophin Gel will be a solid gel when refrigerated; it needs to be warmed to a liquid gel before injecting. Warm the contents of the vial by rolling between your hands for a few minutes. Do not microwave or heat on the stove.

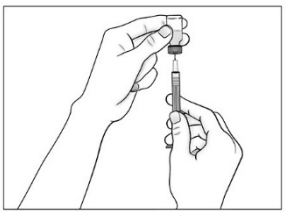


- Remove (flip off) the plastic cap from the top of the Purified Cortrophin Gel vial and throw away this plastic cap in the trash. Do not put the plastic cap back on the vial.



- Wipe the top of the vial rubber stopper with a new sterile alcohol wipe.

- Use a new sterile 20G needle (or needle prescribed for withdrawal) and syringe to draw up the amount of Purified Cortrophin Gel your healthcare provider has told you to use.



Injecting Purified Cortrophin Gel

- Prepare the skin where you are going to give the injection by wiping it with a new sterile alcohol wipe. Allow to air dry.
- Replace the 20G needle (or needle prescribed for withdrawal) used for drawing the Purified Cortrophin Gel from the vial with the 23G needle (or needle prescribed for injection). Do not use the 20G needle for injecting.
- Give the injection the way your healthcare provider has instructed you.
- Return the vial to the refrigerator as soon as possible.

Disposing of your used needles and syringe

- Put your used needles and syringe in an FDA-cleared sharps disposal container right away after use. **Do not** throw away your used needles and syringe in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information

about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

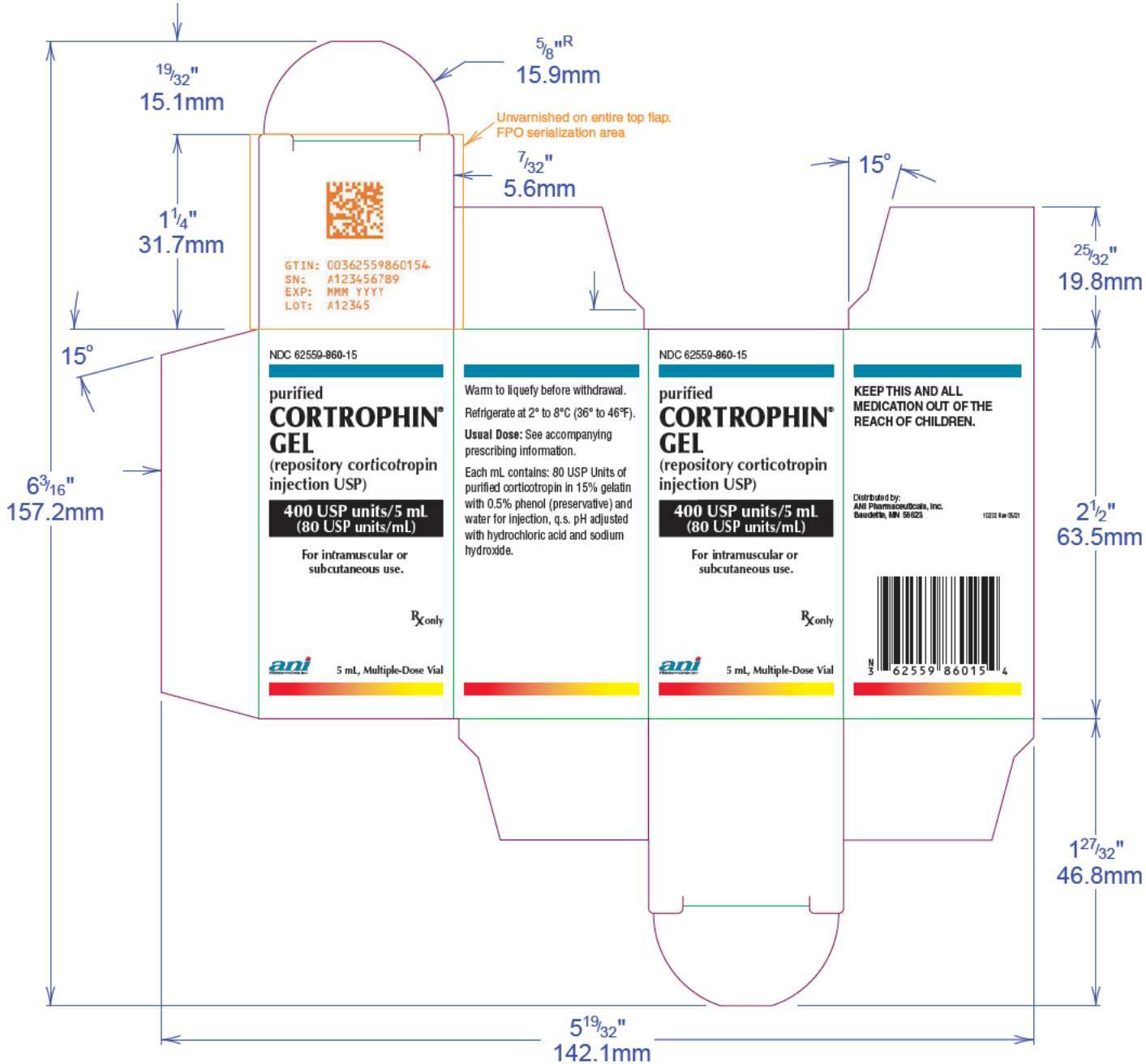
Storing Purified Cortrophin Gel
- Store vials of Purified Cortrophin Gel in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Throw away any vials after the expiration date printed on the label.

Keep Purified Cortrophin Gel and all medication out of the reach of children.

Distributed by: ANI Pharmaceuticals, Inc., Baudette, MN 56623

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: Oct 2021



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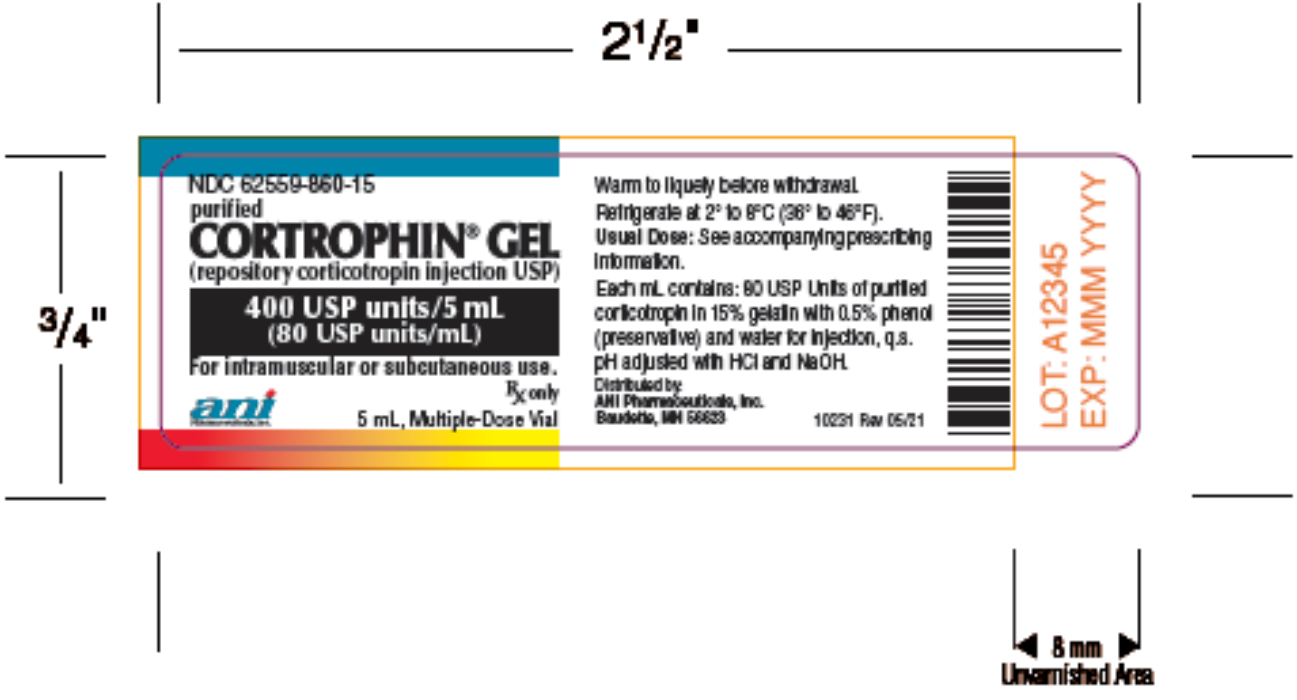
Reference ID: 4880561



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Reference ID: 4880561

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

008975Orig1s008

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	CMC Prior Approval Supplement
Application Number(s)	NDA 008975/ Supplement 8
Priority or Standard	Standard
Submit Date(s)	06/29/2021
Received Date(s)	06/29/2021
PDUFA Goal Date	10/29/2021
Division/Office	Division of General Endocrinology (DGE)
Review Completion Date	10/ 28/2021
Established/Proper Name	Repository corticotropin injection
(Proposed) Trade Name	Purified Cortrophin Gel
Applicant	ANI Pharmaceuticals, INC.
Dosage form	Injection
Applicant proposed Dosing Regimen	For verification of adrenal responsiveness to corticotrophin: 80 units as a single injection Following verification dosage should be individualized according to the disease under treatment and the general medical condition of each patient. Multiple sclerosis: 80-120 units intramuscularly (i.m) for 2-3 weeks
Applicant Proposed Indication(s)/Population(s)	(b) (4) 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, Ankylosing spondylitis, Acute gouty arthritis. Collagen diseases: During an exacerbation or as maintenance therapy in selected cases of Systemic lupus erythematosus, Systemic dermatomyositis (polymyositis) Dermatologic diseases: Severe erythema multiforme (Stevens-Johnson syndrome), Severe psoriasis Allergic states: Atopic dermatitis, Serum sickness Ophthalmic diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as Allergic conjunctivitis, Keratitis, Iritis and iridocyclitis, Diffuse posterior uveitis and choroiditis, Optic neuritis, Chorioretinitis, Anterior segment inflammation Respiratory diseases: Symptomatic sarcoidosis Edematous states: 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

	(b) (4) Nervous system: Acute exacerbations of multiple sclerosis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	As above, (b) (4)
Recommended Dosing Regimen	For verification of adrenal responsiveness to corticotrophin: 80 units as a single injection Following verification dosage should be individualized according to the disease under treatment and the general medical condition of each patient. Multiple sclerosis: 80-120 units intramuscularly (i.m.) for 2-3 weeks

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Mohamad Kronfol, PhD	OCP/DCEP	Authored: Section 6
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Clinical Reviewer	Geanina Roman-Popoveniuc, MD	OCHEN/DGE	Authored: Sections 1, 2, 3, 7, 8, 11
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Deputy Division Director (Clinical)	Naomi Lowy, MD	OCHEN/DGE	Approved: All Sections
	Signature: see DARRTS signature page		

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics

PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

With this CMC Supplement, the Applicant seeks to re-commercialize the product that was withdrawn from the market in 1985.

Purified Cortrophin Gel is a naturally-derived drug product that is extracted from porcine pituitary glands and contains adrenocorticotropin hormone (ACTH; *corticotrophin*) as an active ingredient. According to the approved label, "*Purified Cortrophin Gel is purified corticotrophin (ACTH) in a sterile solution of gelatin for prolonged activity. It is supplied as 80 USP units per mL... Administration is by intramuscular or subcutaneous injection. It is comprised of 39 amino-acids."* ACTH stimulates the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and multiple weakly androgenic substances. Aside of its steroidogenic effect, it is also thought that ACTH exerts its actions via other corticosteroid-independent melanocortin pathways as well, with impact on processes such as inflammation, pigmentation, and immunomodulation that are potentially relevant to autoimmune diseases. [1]

Purified Cortrophin Gel was approved on June 16, 1954, under NDA 008975, for diagnostic testing of adrenocortical function and for treatment of a variety of disorders and diseases that were thought to benefit from steroid-mediated immunosuppression. In 1971, a Drug Efficacy Study Implementation (DESI) review established that Purified Cortrophin Gel is "effective or probably effective" for the diagnostic testing of adrenocortical function and for treatment of various chronic conditions responsive to corticosteroid therapy, such as various rheumatic disorders, dermatologic disease (e.g., Stevens-Johnson syndrome), collagen diseases, allergic states (e.g., allergic rhinitis, bronchial asthma, contact dermatitis), ophthalmologic diseases, respiratory diseases, hematologic disorders, gastrointestinal diseases, neoplastic disorders, edematous states, metabolic disorders, gastrointestinal diseases and other miscellaneous conditions (tuberculosis meningitis, trichinosis of neurological or myocardial involvement). [2] Acute exacerbation of multiple sclerosis was added as an indication in 1977 or 1978 (refer to Division of Neurology review from 11/20/2020 in DARRTS).

Marketing of this product was discontinued for business-related reasons by the application owner at that time (Organon, Inc.) in 1985.

On 03/23/2020, the Applicant (ANI Pharmaceuticals, current owner of this NDA) submitted a Chemistry and Manufacturing Controls (CMC) Prior Approval Supplement (S-008) with the intent to re-commercialize the product. A Refuse to File letter was sent on 04/27/2020, citing

[1] Arnason B., et al. Mechanisms of action of adrenocorticotropic hormone and other melanocortins relevant to the clinical management of patients with multiple sclerosis. Mult Scler J. 2013; 19: 130–136

[2] Federal Register, Vol.36, No 152-Friday, August 6, 1971

several CMC deficiencies related to immunogenicity, virus clearance/validation, drug substance manufacturing and product purity, and lack of essential microbiological information in the application. The Applicant re-submitted a CMC Prior Approval Supplement (PAS) on 06/29/2021. The submission included: 1) detailed CMC data intended to bridge the to-be-marketed product to the originally approved (legacy) product, and 2) immunogenicity risk assessment. In addition, the Applicant submitted a phase 1 pharmacodynamic study in healthy volunteers and a literature review of pharmacodynamic effects of corticotrophin gel including a cortisol response to ACTH stimulation, (b) (4) (b) (4)

1.2. Benefit-Risk Assessment

Purified Cortrophin Gel is a naturally derived drug product that contains ACTH as an active ingredient. It is extracted from porcine pituitary glands. Purified Cortrophin Gel was approved on June 16, 1954, under NDA 008975, for diagnostic testing of adrenocortical function and for treatment of a variety of autoimmune conditions, as well as severe allergic and inflammatory conditions thought to benefit from steroid-mediated immunosuppression. The majority of the indications underwent DESI review in 1971 and/or were added later (multiple sclerosis). Marketing of this product was discontinued in 1985 for business reasons.

The Applicant submitted a CMC PAS (S-008) for Purified Cortrophin Gel, with the intent of re-commercialization of Purified Cortrophin Gel. The submission included CMC data intended to bridge the to-be-marketed Purified Cortrophin gel product to the legacy product. Since the legacy product is not available, the Applicant provided a paper bridging comparison of the proposed drug to the Corticotropin WHO International Reference Standard (WHO-IRS) and to the historical data available for the legacy product. The review of CMC data demonstrated that the Applicant demonstrated sufficient comparability of the to-be-marketed product to the legacy product to support re-commercialization of the discontinued product.

(b) (4) treatment of acute exacerbation of various autoimmune conditions (e.g., multiple sclerosis, rheumatoid arthritis, systemic lupus erythematous, psoriasis, ulcerative colitis, etc.) and the severe manifestation of other dermatologic and ophthalmologic allergic and inflammatory diseases (e.g., Stevens-Johnson syndrome, atopic dermatitis, allergic conjunctivitis, optic neuritis, etc.). Thus, no new clinical data were required and/or included in this submission to demonstrate efficacy and/or safety of the drug (b) (4) maintains consistency within a pharmacologic class (i.e., with H.P. Acthar Gel, the only other naturally derived corticotrophin product available on the market (b) (4) (b) (4)

The labeled adverse reactions (AR) associated with Purified Cortrophin Gel use are well understood and mechanistically anticipated and are due mainly to elevated cortisol levels. These cortisol related ARs are cataracts, glaucoma, infections, elevated blood pressure, edema, hypokalemia, psychiatric complications, growth suppression in children, etc. The Applicant did not propose additional changes to

the drug product safety claims in the label. Since the to-be-marketed product was established to be comparable to the legacy product, no new safety and/or increase in frequency of known ARs is expected with re-commercialized product.

The Purified Cortrophin Gel is a product derived from porcine pituitary gland, and, thus, there is a potential risk of immunogenicity associated with drug use. However, as per CMC review, based on the comparability data provided in the supplement, the immunogenicity of the -to-be-marketed product is not expected to be higher compared to the legacy product. The potential immunogenicity risk of Purified Cortrophin Gel will be adequately mitigated through labeling. However, the Applicant should continue monitoring for the immunogenicity-related safety signals in the postmarketing settings. Lastly, if the Applicant considers pursuing the drug development for a new indication(s) in the future, the risk of immunogenicity should be adequately evaluated in clinical studies.

Office of Pharmaceutical Manufacturing Quality has determined the manufacturing facilities are acceptable.

In conclusion, the Applicant successfully bridged the to-be-marketed product to the legacy product that has been discontinued in 1984 NOT for efficacy and/or safety reasons. Thus, the Division recommends approval of this supplement.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Purified Cortrophin Gel was approved in 1954 for the adrenocortical function testing and for the treatment of a wide range of the diseases and conditions. The drug product contains ACTH that stimulates adrenal gland and increases synthesis of cortisol and other adrenocortical hormones. • A Drug Efficacy Study Implementation (DESI) review of the original indications in 1971 concluded that the drug is effective or probably effective for the indications (b) (4) i.e. diagnostic testing of adrenocortical function, treatment of psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis, systemic lupus erythematosus, systemic dermatomyositis, Stevens-Johnson syndrome, psoriasis, atopic dermatitis, serum sickness, allergic conjunctivitis, keratitis, iritis and iridocyclitis, posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation, symptomatic sarcoidosis, proteinuria in the nephrotic syndrome, ulcerative colitis, acute exacerbations of multiple sclerosis. The indication for the treatment of multiple sclerosis was added in 1977.	Purified Cortrophin Gel is approved for the adrenocortical function testing and for the treatment of wide range of the disease and conditions that were thought to benefit from steroid-mediated suppression.
Current Treatment Options	• Short-acting injectable synthetic ACTH formulations are FDA-approved and currently recommended by scientific society guidelines[3] for diagnostic testing of adrenocortical function. • Corticosteroid therapy (e.g., prednisone, methylprednisolone, dexamethasone, etc.) is considered the treatment of choice for acute exacerbation of autoimmune conditions, severe dermatologic and ophthalmologic allergic and inflammatory conditions. • H.P. Acthar Gel (NDA 022432) is another purified corticotrophin	Short-acting injectable synthetic ACTH formulations are the standard of care for diagnostic testing of adrenocortical function. Corticosteroid therapy is the treatment of choice for the acute exacerbation of autoimmune conditions and other severe allergic and inflammatory states.

[3] Bornstein SR, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016;101(2): 364-389

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	product currently available on US market and is indicated for the treatment of the various conditions thought to benefit from steroid-mediated immunosuppression, in subjects who are not able to tolerate steroid therapy.	H.P. Acthar Gel is the only other purified corticotrophin product that is currently available on US market for the treatment of are generally recommended in subjects who are not able to tolerate steroid therapy.
Benefit	• The efficacy of Purified Cortrophin Gel for the treatment of acute exacerbation of various autoimmune conditions and severe dermatologic and ophthalmologic allergic and inflammatory conditions mentioned above has been established following a DESI review in 1971. (b) (4)	The benefit of Purified Cortrophin Gel for the treatment of acute exacerbation of various autoimmune conditions and severe dermatologic and ophthalmologic allergic and inflammatory conditions as listed in the current label has been established following a DESI review in 1971. The indication for the treatment of multiple sclerosis was approved in 1977. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The labeled adverse reactions for the drug are well understood and are based on its mechanism of action to stimulate cortisol secretion. These cortisol related ARs include various ophthalmologic reactions, hypertension, edema, hyperkalemia, delayed growth in children, infectious, etc. • No new safety signals have become available from post-marketing reports. • There is a potential risk of immunogenicity, since the drug product is a purified hormonal product derived from porcine pituitary gland. However, CMC reviewers concluded that no increase in immunogenicity is expected with use of to-be-marketed product compared to the legacy product. The risk can be mitigated through the product labeling.	No changes to the current label safety information were proposed by the Applicant. The potential immunogenicity risk will be adequately mitigated through the product labeling at this time. Immunogenicity -related adverse reactions should be closely monitored in the post-marketing settings. Should the Applicant pursue additional indication(s) in the future, the immunogenicity risk of the drug should be addressed in the development program.

2 Therapeutic Context

2.1. Analysis of Condition

[redacted] (b) (4).

Adrenal insufficiency (AI) is a serious and life-threatening condition if left untreated. Early diagnosis of AI is required to correctly identify individuals who require immediate treatment with glucocorticoids to prevent morbidity and mortality associated with AI.

Autoimmune conditions encompass a wide variety of diseases characterized by immune-mediated chronic inflammation which can involve one, or multiple system organ classes. Examples of such conditions include nervous system disorders (i.e., multiple sclerosis), rheumatological disorders (i.e., psoriatic arthritis, rheumatoid arthritis, ankylosis spondylitis, systemic lupus erythematous, etc.), respiratory diseases (e.g., symptomatic sarcoidosis), and gastrointestinal diseases (i.e., ulcerative colitis). These conditions, if left untreated, are generally associated with high morbidity and mortality. Acute exacerbations of such conditions are known to be responsive to corticosteroid therapy. Corticosteroid therapy is also a mainstay therapy in other severe inflammatory conditions such as dermatologic diseases (e.g., erythema multiforme), allergic states (e.g., atopic dermatitis, serum sickness), ophthalmologic diseases (e.g., allergic conjunctivitis, keratitis, optic neuritis, etc.), and edematous states.

2.2. Analysis of Current Treatment Options

The gold standard test for the diagnosis of AI is the ACTH stimulation test using a standard high-dose of short-acting (or immediate-release) ACTH (250 mcg). Current medical practice and scientific society guidelines[4] recommend measurement of cortisol levels at 30- and 60-minutes following administration of short-acting (immediate-release) cosyntropin at a dose of 250 mcg. An adequate response is defined by a peak cortisol level of at least 18 mcg/dL (497 nmol/L) after 30 or 60 minutes of cosyntropin administration. Multiple immediate-release injectable synthetic ACTH formulations are approved in a single dose of 250 mcg as a diagnostic agent for this ACTH stimulation test and are currently available on US market. [redacted] (b) (4)

Corticosteroid therapy (e.g., prednisone, methylprednisolone, dexamethasone) is generally recommended for treatment of acute exacerbation of autoimmune conditions (e.g., multiple sclerosis, psoriatic arthritis, rheumatoid arthritis, ankylosis spondylitis, systemic lupus

[4] Bornstein SR, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016;101(2): 364-389

erythematous, sarcoidosis, ulcerative colitis, etc.) and/or severe inflammatory conditions (e.g., erythema multiforme, allergic states, edematous states, etc.).

The only other naturally derived corticotrophin product currently on the US market is H.P. Acthar Gel (NDA 008372). It is indicated for treatment of acute exacerbation of autoimmune and/or severe inflammatory conditions in subjects who are not able to tolerate corticosteroids. H.P. Acthar Gel was approved in 1951 and underwent DESI review in 1971. Following the DESI review, H.P. Acthar Gel and Purified Cortrophin Gel had the same approved indications in their corresponding labels.

In 2010, Questor (H.P. Acthar Gel owner) voluntarily removed some indications from the H.P. Acthar Gel label due to the lack of clinical evidence supporting the safety and efficacy of the drug in these indications. The removed indications were: all neoplastic conditions, all endocrine disorders including adrenocortical function testing, all hematologic disorders, Loeffler's syndrome, berylliosis, fulminant or disseminated pulmonary tuberculosis, aspiration pneumonitis, pemphigus, bullous dermatitis, exfoliative dermatitis, seborrheic dermatitis, mycosis fungoides and "miscellaneous conditions". Currently, H.P. Acthar Gel is approved for 19 indications.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Purified Cortrophin Gel was approved on June 16, 1954, under NDA 008975 for diagnostic testing of adrenocortical function and for treatment of a variety of disorders and diseases that at the time were thought to benefit from steroid-mediated immunosuppression, including various rheumatologic, dermatologic, ophthalmic, hematologic, endocrine, etc., conditions (see the list of the approved indications below).

The initial approval of Purified Cortrophin Gel occurred prior to the Kefauver-Harris amendment to the Federal Food, Drug and Cosmetic Act of 1962, which introduced the requirement of "substantial evidence" of two adequate and well controlled trials. At the time of the original approval, drug manufacturers only had to show the drug was safe for use in humans, with limited data required to demonstrate efficacy. These data would be grossly inadequate to support approval of a new drug or new indications by the Agency under current standards requiring evidence from adequate and well-controlled clinical trials.

A Drug Efficacy Study Implementation (DESI) review of corticotrophin products including Purified Cortrophin Gel and H.P. Acthar Gel was initiated in 1971 and finalized in 1977. Changes

to the package insert of Purified Cortrophin Gel following DESI review in 1971 included the following[5]:

Purified Cortrophin® Gel (Repository Corticotropin Injection) is indicated for diagnostic testing of adrenocortical function.

Purified Cortrophin® Gel (Repository Corticotropin Injection) has limited therapeutic value in those conditions responsive to corticosteroid therapy, however, corticosteroid therapy is considered to be the treatment of choice. Purified Cortrophin® Gel (Repository Corticotropin Injection) may be employed in the following disorders:

1. *ENDOCRINE DISORDERS - Nonsuppurative thyroiditis; Hypercalcemia associated with cancer*
2. *RHEUMATIC DISORDERS – As adjunctive therapy for short-term administration to tide the patient over an acute episode or exacerbation; Psoriatic arthritis; Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); Ankylosis spondylitis; Acute and subacute bursitis; Acute nonspecific tenosynovitis; Acute gouty arthritis; Synovitis or osteoarthritis; Epicondylitis*
3. *COLLAGEN DISEASES – During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus; Systemic dermatomyositis (polymyositis); Acute rheumatic carditis*
4. *DERMATOLOGIC DISEASES – Pemphigus; Bullous dermatitis herpetiformis; Severe erythema multiforme (Stevens-Johnson syndrome); Exfoliative dermatitis; Severe psoriasis; Severe seborrheic dermatitis; Mycosis fungoides.*
5. *ALLERGIC STATES – Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: Seasonal or perennial; allergic rhinitis; Bronchial asthma; Contact dermatitis; Serum sickness.*
6. *OPHTHALMOLOGIC DISEASES – Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: Allergic conjunctivitis; Keratitis; Herpes zoster ophthalmic; Iritis and iridocyclitis; Diffuse posterior uveitis and choroiditis; Optic neuritis; Chorioretinitis, Anterior segment inflammation.*
7. *RESPIRATORY DISEASES – Symptomatic sarcoidosis; Loeffler's syndrome; Berylliosis; Fulminant or disseminated pulmonary tuberculosis when used concurrently with antituberculosis chemotherapy; Aspiration pneumonitis.*
8. *HEMATOLOGIC DOSORDERS – Acquired hemolytic anemia; Secondary thrombocytopenia in adults; Erythroblastopenia; Congenital hypoplastic anemia*
9. *NEOPLASTIC DISEASES - For palliative management of leukemias and lymphomas in adults*
10. *EDEMATOUS STATES – To induce a diuresis of a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematous*
11. *GASTROINTESTINAL DISEASES - To tide the patient over a critical period of the disease in: ulcerative colitis, regional enteritis*

[5] Federal Register, Vol.36, No 152-Friday, August 6, 1971

12. *MISCELLANEOUS – Tuberculous meningitis with subarachnoid block or impending block when used concurrently with antituberculosis chemotherapy; Trichinosis with neurologic ort myocardial involvement.*

Indication for treatment of multiple sclerosis was approved in 1977.

Marketing of Purified Cortrophin Gel was discontinued in 1985 by the application owner at the time, Organon, Inc for business reasons.

3.2. Summary of Presubmission/Submission Regulatory Activity

On January 4, 2016, ANI Pharmaceuticals, Inc. (ANI) acquired ownership of NDA 008975 for Purified Cortrophin Gel from Merc Sharp & Dohme Corporation (NDA's owner at that time).

On December 29, 2017, ANI Pharmaceuticals (Applicant) requested a Type C meeting to discuss their proposed strategies to support the re-commercialization of this product. A Written Responses Only letter was issued on March 15, 2018. The Agency indicated that the Applicant needs to bridge and to demonstrate that the change their propose does not adversely affect the quality of the drug product with respect to efficacy, quality, and safety. The Agency recognized that this might be challenging since the drug has not been marketed for over 30 years. Typically, this is done by specification.

A teleconference between the Applicant and the Agency was held on May 3, 2018. The Agency recommended the Applicant the following: 1) provide adequate comparative analytical data for the to-be-marketed product and the legacy product to ensure similarity in efficacy between the two products; 2) address how the safety of the to-be-marketed product may be affected by potential differences between the two products (e.g., differences in the impurity and degradant profiles, ACTH, as well as other active and inactive ingredient concentrations); 3) consider analogous updates to the label according to the recently updated H.P. Acthar Gel package insert.

On March 23, 2020, the Applicant submitted a Prior Approval Supplement (PAS) (S-008) to NDA 008975 to re-introduce Purified Cortrophin Gel to the market. A Refusal to File letter was issued on April 27, 2020, due to the multiple Chemistry, Manufacturing and Controls (CMC) deficiencies as follows: 1) absence of immunogenicity risk assessment; 2) viral clearance/validation issues; 3) drug substance manufacturing issues; 4) microbiology issues.

The Applicant requested a teleconference on September 23, 2020, to obtain concurrence on the CMC data package to be included in the supplemental NDA for the re-introduction of Purified Cortrophin Gel into the US market. A teleconference meeting between the Agency and the Applicant was held on December 15, 2020 to discuss the deficiencies in the Refuse to File letter. The Applicant proposed (b) (4) preservation of legacy format. Additionally, the Applicant inquired about (b) (4) The

Agency stated that discussion regarding the labeling content was premature without reviewing the data supporting the labeling changes, but the Applicant was made aware that if a bridge between the current product formulation and the previously marketed formulation is established (b) (4) (b) (4) . Thus, the Agency recommended the Applicant to provide the necessary information, including immunogenicity, supporting safe use of the product for the proposed indications.

On June 29, 2021, the Sponsor submitted a CMC PAS which included 1) detailed CMC data to bridge the proposed product to the originally approved product, and 2) immunogenicity risk assessment. In addition, the submission included a clinical phase 1 pharmacodynamic study in healthy volunteers and literature review of cortisol response to cortrophin gel formulations, as supportive data. The Applicant revised the old label and proposes to include the following indications in the label:

(b) (4)

Purified Cortrophin Gel may be employed in the following disorders:

1. 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.
Acute gouty arthritis.
2. COLLAGEN DISEASES:
During an exacerbation or as maintenance therapy in selected cases of:
Systemic lupus erythematosus.
Systemic dermatomyositis (polymyositis).
3. DERMATOLOGIC DISEASES:
Severe erythema multiforme (Stevens-Johnson syndrome).
Severe psoriasis.
4. ALLERGIC STATES:
(b) (4)
Atopic dermatitis.
Serum sickness.
5. OPHTHALMIC DISEASES:
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
Allergic conjunctivitis.

Keratitis.
Iritis and iridocyclitis.
Diffuse posterior uveitis and choroiditis.
Optic neuritis.
Chorioretinitis.
Anterior segment inflammation.
6. RESPIRATORY DISEASES:
Symptomatic sarcoidosis.
7. EDEMATOUS STATES:
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.

(b) (4)

9. NERVOUS SYSTEM:
Acute exacerbations of multiple sclerosis.

(b) (4)

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical studies for the regulatory purposes were performed to support this application. Therefore, no inspections of clinical sites were necessary.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) team recommends Approval (see Division of Postmarketing Activities, Office of Lifecycle Drug Products, OPQ Review dated 10/25/2021). The Office of Pharmaceutical Manufacturing Assessment (OPMQ) has determined that the manufacturing facilities are acceptable (refer to review from October 25, 2021). There are no outstanding CMC deficiencies related to the drug substance or drug product for this supplement.

[6] We update guidances periodically. For the most recent version of guidance, check the FDA guidance web page https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In 2016, ANI acquired ownership of NDA 008975 from Merck Sharp & Dohme Corporation and of all documentation related to DMF # (b) (4) for the drug substance corticotrophin from (b) (4). The Applicant's strategy for re-commercialization of the product was to limit changes to the approved drug substance and drug product manufacturing processes, while ensuring that the processes are compliant with current quality practices and regulatory expectations. CMC and QTR reviewers concluded that the Applicant has implemented an adequate control strategy (b) (4) (b) (4) derived from that complex process. The product has not been on the market for over 35 years, and the drug substance and drug product from the previous NDA holder were not available. For that reason, the Applicant was not able to directly compare the proposed and legacy products. Thus, the Applicant provided a "paper comparison" that includes data on comparability of the products by retrospective comparison to historical data comprising of in-process data, characterization data, release data, and stability data. The analytical or "paper bridge" approach was discussed on multiple occasions between the Agency and the Applicant (refer to the Regulatory Background Section above). FDA informed the Sponsor that the acceptability of the approach depended on a reliable bridge, and additional efficacy or safety data could potentially by required.

CMC reviewers reviewed the data provided in this submission and concluded that the Applicant demonstrated sufficient comparability between the to-be-marketed product and legacy product. The reviewer also noted that the Applicant made improvements to the manufacturing process and analytical methodology.

According to the CMC reviewer, the Applicant provided a bridging comparison of the proposed drug substance from (b) (4) to the Corticotropin WHO International Reference Standard (WHO-IRS), which is considered very stable. The legacy product also relied on the WHO standard. The reviewer confirmed that using the WHO standard material as a bridging reference, the analytical data demonstrate that the (b) (4) and legacy drug substances have comparable (b) (4) profiles.

The active ingredient in the drug substance preparation, ACTH (1-39), is approximately (b) (4) (b) (4) (b) (4). However, the Applicant did not attempt to deviate from legacy process steps in order to claim comparability. At the suggestion of the Agency, the Applicant monitored bioburden and bacterial endotoxin levels (b) (4)

(b) (4)

The drug product is supplied as 80 USP units per mL and contains 0.5% phenol as preservative and 15.0% gelatin for prolonged activity. The drug product is supplied as a sterile, (b) (4) (b) (4), multi-dose product containing 0.5% phenol and 15.0% gelatin which is pH adjusted with hydrochloric acid and/or sodium hydroxide. The product is administered *via* intramuscular or subcutaneous injection without further dilution.

Purified Cortrophin Gel is supplied in a 5 mL, (b) (4) glass vial that is closed with a gray (b) (4) (b) (4) stopper and aluminum overseal. The fill volume of the drug product is targeted at (b) (4) mL to provide a withdrawable volume of 5.0 mL.

The Applicant submitted stability data up to 24 months at long-term storage condition and was found to be acceptable by the reviewer.

The Applicant proposed to introduce (b) (4) as a new drug substance manufacturer, (b) (4) as a new drug product manufacturer and (b) (4) as a new testing and release site, since the old manufacturing sites manufacturers were no longer in operation. The inspection of the facilities was completed and OPMA reviewer recommends approval of the supplement.

The Applicant submitted a claim for a Categorical Exclusion from the requirement of an Environmental Impact Statement (EIS) for this supplement as per 21 CFR 25.31 (refer to the Applicant's amendment in Section 1.12.14 submitted on October 27, 2021). The Applicant claims that to their knowledge no extraordinary circumstances exists and no environmental assessment needs to be performed. CMC reviewer granted the Applicant's request for Categorical Exclusion from the Environmental Analysis and recommends approval of the amended supplement (refer to CMC review from October 27, 2021).

4.3.Clinical Microbiology

Microbiology reviewer, Dr. Ericka Pfeiler, concluded that the Applicant provided adequate information, including sterility assurance, in this supplement in order to reintroduce Purified Cortrophin Gel to the market (refer to review from 9/23/2021).

4.4.Immunogenicity

Purified Cortrophin Gel is a potentially immunogenic product due to its animal source. Thus, an immunogenicity risk assessment was requested by the Agency and submitted by the Applicant to support the supplement. The Division consulted the Office of Biotechnology Products (OBP) to review the immunogenicity risk assessment.

OBP reviewers noted that the to-be-marketed product carries a potential risk of immunogenicity, and the submitted data are insufficient to characterize the immunogenicity of the to-be-marketed product itself.

OBP reviewers indicated that the immunogenicity potential of the to-be-marketed product was compared to that of the WHO international reference standard (IRS) for ACTH as a part of an overall bridging comparison of the proposed drug substance to legacy substance (see discussion above). No direct comparison of the immunogenicity was made between the legacy product and to-be marketed product since the legacy material of the product is not available. The reviewers noted that there was an (b) (4) (b) (4) in the to-be-marketed product in comparison to WHO-IRS. However, the reviewers also noted (b) (4) using a substitution method. It's not clear how reliable this method would be for prediction of (b) (4) (b) (4) (b) (4). Therefore, there is residual uncertainty on the potential for immunogenicity Thus, the potential impact of these differences on immunogenicity of the product remains unknown. (b) (4)

The Applicant also stated that "using WHO standard material as a bridging reference, the analytical data demonstrate that the (b) (4) and legacy drug substances have comparable (b) (4) profiles".

In addition, OBP reviewers also noted that the (b) (4) , can also impact immunogenicity. However, no historical data were provided for the legacy product, thus it remains unknown whether the legacy product contained (b) (4) The CMC reviewer also noted that (b) (4) (b) (4) and it is extremely challenging to rely on quantitative differences in Area% (quantitation of area under each peak in the chromatogram by RP-HPLC). OBP is accurate in pointing out that it is impossible to know (b) (4) that may pose a higher risk to immunogenicity in comparison to legacy product". In this context it should also be noted (b) (4) (b) (4) compared to applicant's APIs suggesting that applicant managed to reduce (b) (4) concern for immunogenicity".

Thus, due to all above uncertainties, the OBP and CMC reviewers concluded that, although, there is a potential immunogenic risk, it is most likely not higher than risk associated with use of the legacy product. The immunogenicity was never evaluated for the legacy product; however, the legacy product was on the US market since 1954, was found to be effective for the

proposed indications during the DESI review. In addition, the clinical review of published literature and available administrative records did not identify concerning safety reports. Lastly, the risk of immunogenicity is monitorable and adequately described in the proposed labeling.

The Division agrees that the Applicant should continue to monitor for the potential immunogenicity safety issues in postmarketing settings. If the Applicant plans to pursue a new indication(s) in future, the appropriate elevation of immunogenicity should be included in the clinical study(s) for the new indication(s).

5 Nonclinical Pharmacology/Toxicology

No pharmacology/toxicology data was included in this submission.

6 Clinical Pharmacology

6.1.Executive Summary

Purified Cortrophin Gel 80 units/mL multi-dose vial is a naturally derived drug product, of which the active ingredient, corticotropin, is extracted from porcine pituitary glands. With the Supplement, the Applicant also submitted results of a phase 1 open label 1-period pharmacodynamic (PD) study and a separate report comparing the results to those of 10 studies with historical cortisol PD data published in the literature. The division regarded the PD data as supportive to the CMC data submitted. OCP's review of the PD study results and the literature is outlined in this document.

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

ANI completed a Phase I study CA28049 to assess the effect of a single intramuscular (IM) dose of its to-be-marketed Purified Cortrophin Gel on cortisol release in healthy adult subjects and conducted a comparative analysis of the pharmacodynamic (PD) responses from its to-be-marketed product in Study CA28049 to those reported in the scientific literature for corticotropin products. Study CA28049 shows that cortisol levels were significantly increased above the baseline levels. The Applicant attempted to assess comparability of the cortisol response from Study CA28049 to that reported in literature. However, there are several limitations of using such approach (see section 6.3). The primary bridging data of the proposed to-be-marketed product to the previously marketed product will be based on analytical characterization. The clinical PD study is considered supportive in nature. The PD data provides a confirmation of the in vivo pharmacological activity of the proposed product as indicated by the cortisol release.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Purified Cortrophin Gel (repository corticotropin injection) is administered as a single 80-unit intramuscular injection (IM).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Study CA28049:

ANI's Purified Cortrophin gel is administered by intramuscular injection (IM) providing sustained corticotropin into the systemic circulation and subsequently a sustained release of cortisol by the adrenal glands.

Adrenocorticotropic hormone (ACTH, also known as corticotropin) is rapidly hydrolyzed by endogenous proteases in the bloodstream following a bolus intravenous injection (IV) resulting in a plasma half-life of about 15 minutes. The pharmacodynamic (PD) effect (cortisol level) was measured following administration of ANI purified corticotropin gel.

ANI conducted an open-label, 1-period PD study (CA28049) with a single 80-unit dose of Cortrophin gel administered via IM injection in 20 normal healthy volunteers. The objective was to assess the effect of a single IM dose of Cortrophin Gel on cortisol levels. Serial plasma cortisol concentrations were measured for 24 hours before dosing, in order to establish baseline concentrations, as well as for 24 hours post-dose. The sampling times were pre-dose, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8-, 10-, 12-, and 24-hours post-dose.

The mean (SD) plasma Cortisol concentration for Day -1 (baseline) and Day 1 (Unadjusted and baseline-corrected) are shown in **Figure** 1. Summary plasma cortisol PD parameters are presented in **Table 1.**

Figure 1. Mean (SD) baseline, unadjusted, and baseline-corrected plasma cortisol concentration-time profiles before (Day -1) and after (Day 1 unadjusted and Day 1 baseline-corrected) a single intramuscular injection of Cortrophin gel 80 units (linear scale) (source: figure 14.2.2.1 on age 54 of the study CA28049 report).

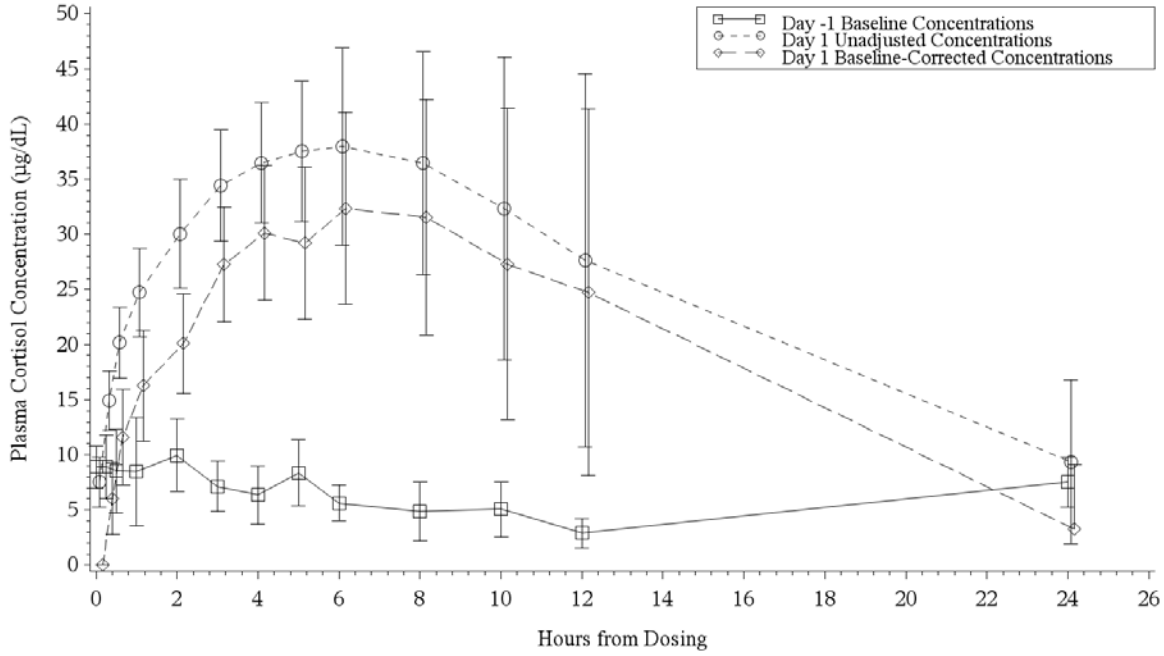

Table 1. Summary of baseline, unadjusted, and baseline-corrected plasma cortisol PK/PD parameters before (Day -1) and after (Day 1 unadjusted and Day 1 baseline-corrected) a single intramuscular injection of Cortrophin gel 80 units (source table 11-2 on page 34 of the study CA28049 report).

PK/PD Parameters (CV%)	Day -1 Baseline	Day 1 Unadjusted	Day 1 Baseline-Corrected
AUC0-24 (µg*hr/dL)	134.9 (23.5) [n=20]	NA	NA
Cmax (µg/dL)	11.87 (29.9) [n=20]	NA	NA
Tmax (hr)*	1.999 (0.00, 23.93) [n=20]	NA	NA
AUEC0-24 (µg*hr/dL)	NA	581.7 (33.8) [n=20]	434.0 (46.3) [n=20]
Emax (µg/dL)	NA	40.55 (19.6) [n=20]	34.52 (28.2) [n=20]
TEmax (hr)*	NA	6.000 (2.00, 12.00) [n=20]	8.002 (3.00, 12.02) [n=20]
*T(E)max values are presented as median (min, max). AUC0-24, Cmax, and Tmax were calculated from Day -1 baseline (endogenous) cortisol concentrations. NA: Not applicable			

The Applicant concluded that the administration of a single IM injection of Cortrophin Gel resulted in cortisol concentrations substantially above the baseline concentrations and the overall (AUEC0-24) and peak (Emax) exposures show marked effect in stimulating endogenous cortisol production and release.

Summary of Bioanalytical Method Validation

Validation study report for the Electrochemiluminescence assay bioanalytical method to measure cortisol in human serum or plasma for Study CA28049 is acceptable (Validation Study ZZ00994-01). The method was validated for limit of quantitation (LOQ), quality control (QC) inter- and intra-Batch precision and accuracy, and long-term, bench-top, freeze-thaw and refrigerator stability (Table 2).

Table 2. Summary of bioanalytical method validation of cortisol in human serum or plasma.

Information Requested	Data
Validation Summary	(b) (4) Validation Study ZZ00994-01
Analyte	Cortisol
Method Description	Electrochemiluminescence
Limit of Quantitation (mg/dL)	1.24 µg/dL
Standard Curve Concentrations (mg/dL)	1.24, 13.08, 14.44, 21.95, and 28.88 µg/dL
QC Concentrations (mg/dL)	L1 = 1.92 µg/dL, L2 = 15.03 µg/dL, L3 = 27.46 µg/dL
QC Intra-Batch Precision Range (% CV)	2.4 to 3.3%
QC Intra-Batch Accuracy Range (% Bias)	100.0 to 100.1%
QC Inter-Batch Precision Range (% CV)	1.5 to 2.6%
QC Inter-Batch Accuracy Range (% Bias)	99.6 to 103.0%
Bench-Top Stability (Hrs)	Short-Term Stability: 26 hours, 23 min (b) (4) with samples stored at ambient temperature (b) (4) (b) (4)
Refrigerator Stability (Hrs)	Refrigerator Stability: 6 days, 23 hours, (b) (4) with samples stored at 5°C.
Freeze-Thaw Stability (Cycles)	4 freeze (-20°C)-thaw (ambient temperature) cycles (b) (4) (b) (4)
Long-Term Storage Stability (Days)	Long-Term Stability: 29 days (b) (4) at -20°C

Source: page 8 of the Bioanalytical Method Validation ZZ00994-01

Study PT-2021-019:

ANI performed a literature search for cortisol-response PD studies following administration of corticotropin and selected those that met the following criteria for further comparison to its product:

- Use of natural porcine corticotropin (i.e., no data from corticotropin derived from other species or prepared synthetically were included).
- Use of gel formulation (no data from zinc-based formulations were included)
- Dose administered in the range 40 – 80 units
- Single dose administration (data from the first dose administered to a subject or, for crossover designs having at least a 72-hour washout, data a subsequent dose administered to a subject were also included).

- Intramuscular (IM) or subcutaneous (SC) administration (no data from intravenous administration were included).
- Studies must have had time zero cortisol concentrations reported to enable baseline correction.

According to the Applicant, a total of 10 published studies met these criteria and are Bayliss (1954), Besser (1967), Brombacher (1969), Danowski (1981), el-Shaboury (1968), Glick (1969), Lal (2016), Nelson (1968), Siegel (1958), and Treadwell (1969). These 10 studies included 110 subjects.

The studies employed designs that differed from each other and from the CA28049 study, in dose levels, sampling times, and sample collection frequencies, making any sort of direct comparison with the CA28049 study impossible. However, considering the complexities of the cortisol pharmacodynamic measurements, applying a population pharmacokinetic type of analysis was not possible.

The limitations of the cortisol-response pharmacodynamic data in the 10 studies made ANI compare the CA28049 data with data from 10 studies using interpolation and extrapolation approach with weighing schemes to re-build the subject level PK/PD profiles from the 10 studies to reflect what would have been expected if the published studies had been designed like the CA28049 study.

The first step estimated the concentrations in the published studies at the same sampling time points used in the CA28049 study via interpolation or extrapolation to rebuild the PD profiles. The second step was to baseline-correct these completed (estimated) PD profiles by subtracting the time zero cortisol concentration from all of the post-dose concentrations. Finally, if the published study employed a dose other than 80 units, the entire baseline-corrected PD profile was dose adjusted to an 80-unit dose to put it on equal footing with the CA28049 study. This process yielded complete cortisol-response PD profiles from each of the published studies representing an estimate of what each published PD profile would have looked like, had the published study been designed like the CA28049 study, i.e., using the same sampling times and the same 80-unit dose level. ANI reports the weighted mean of all studies PD parameters and compares them to that from Study CA28049 (Figure 1**,** Table 3). ANI concluded that Corticotrophin gel matched the cortisol responses from the reconstructed profiles very well, both graphically (Figure 2), and with estimated weighted geometric mean PD parameters Cmax and AUC (Table 3).

Conclusion

Although the Applicant concludes that Purified Cortrophin Gel product elicits cortisol response profiles comparable to those reported in the scientific literature for the same (b) (4) corticotropin gel products, these data cannot constitute a direct standalone PD bridge because of several limitations of the historical data.

The limitations are (1) the complexity of naturally derived drug products makes any definitive conclusion on cross-study comparability difficult, even with dose normalization, because of possible confounders like discrepancies in formulation composition, and heterogeneity of study population between the studies, (2) the inclusion of data from SC and IM rather than IM alone, makes comparison difficult due to potential differences between absorption process between the two routes, (3) baseline cortisol adjustment to endogenous cortisol is not consistent between study CA28049 data (time-matched subtraction) and the literature data (subtraction from concertation at time zero) making the comparison between the two difficult, and (4) assumption of linearity of PD response.

Figure 2. ANI Purified Cortrophin Gel and weighted mean of all studies in database (baseline corrected and dose-adjusted) (Source page 26 of Study PT-2021-019 report)

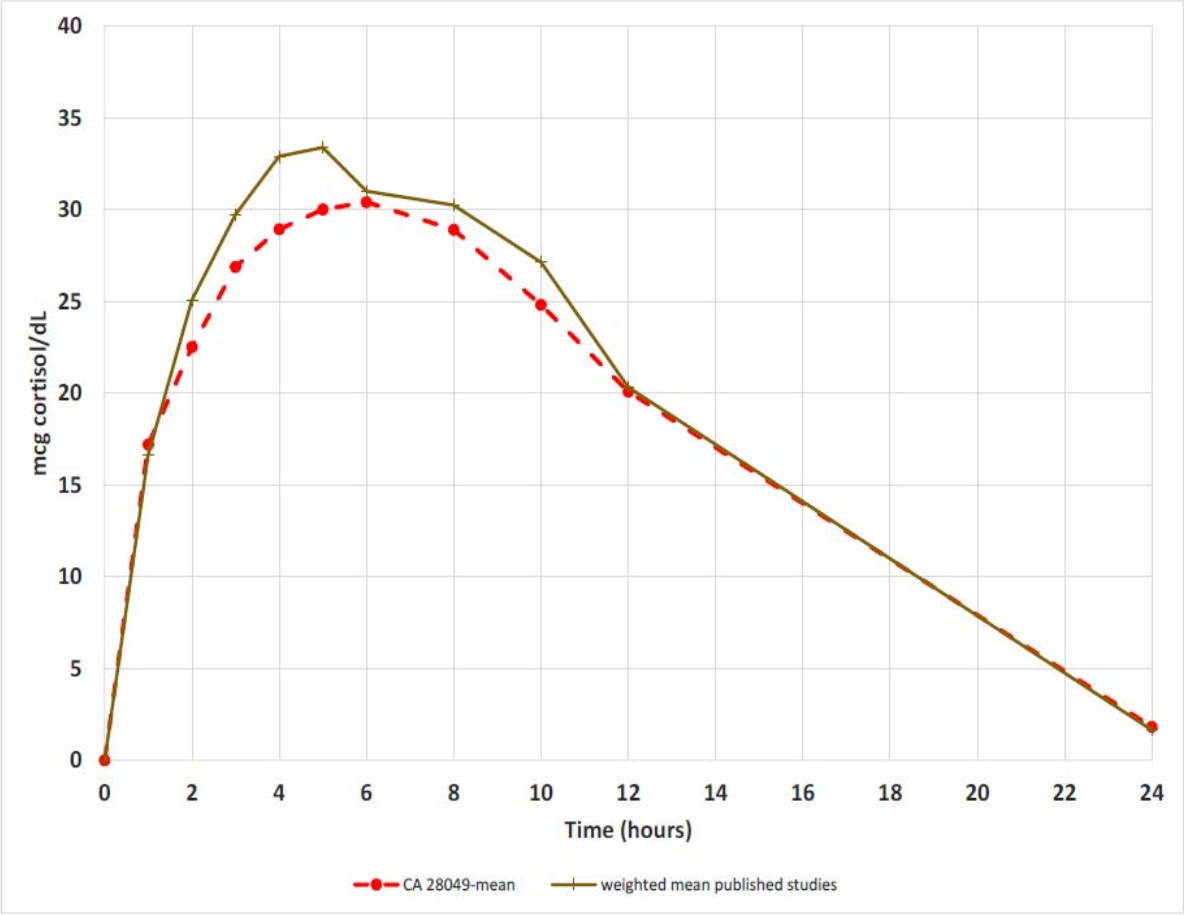

Table 3. Summary PD Parameters from Studies in Database (Source page 39 of Study PT-2021-019 report)

Study	GM C_{max}	GM AUC_t	Arithmetic Mean t_{max}
Weighted mean of published studies	32.09	310.57	5.35
ANI CA28049 Study*	32.96	346.65	7.06
ANI as % of weighted mean of published studies	102.7%	111.6%	131.8%

* Cmax, AUCt, and tmax were calculated using only the PD Analysis Time Points (0, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours), and using only the 0 hour cortisol concentration for baseline correction. Therefore, these values differ from those presented in the clinical study report for the CA28049 study, which included 0.25 and 0.5 hour sampling times, and used a point-by-point baseline correction method.

6.3.2. Clinical Pharmacology Questions

1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

No. The PD study was an open label single dose study that along with the literature comparison, is considered supportive to the CMC information without additional evidence of effectiveness.

2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing is consistent with that of original NDA.

7 Sources of Clinical Data and Review Strategy

The Applicant provided the results from study CA28049 and published literature from studies that evaluated pharmacodynamic effects (cortisol, cortisol precursors, other adrenocortical hormones) of various ACTH formulations. However, these data were not required for the re-establishment of safety and/or efficacy of the drug or provided additional evidence of the efficacy or safety of the drug in the proposed indication. The only data deemed necessary to reintroduce the drug to the market was CMC bridging data of the proposed to-be-marketed product to the legacy product. The efficacy of the legacy product for the proposed indications was established during the DESI review in 1971. Since the Applicant demonstrated the comparability between the to-be-marketed drug and legacy drug, the efficacy and safety of the re-introduced drug and legacy drug is expected to be the same.

The results of CA28049 are discussed in section 6.3.1 above.

7.1. Review Strategy

Although the drug was found to be effective for all proposed indications during DESI review in 1971, the Division compared the proposed Purified Cortrophin label with H.P. Acthar Gel label

for the consistency across the pharmaceutical class. [redacted] Lastly, since the indication for the treatment of multiple sclerosis was added after the DESI review, the Division of Neurology (DN 2) was asked to evaluate if the indication is in accordance with the current clinical practice guidances (refer to Dr. Laura Baldassari's Consult Review in DARRTS dated September 14, 2021).

8 Statistical and Clinical and Evaluation

8.1. Review of Published Data

8.1.1. Review of Published Literature Data to evaluate the Efficacy of the Drug for [redacted]

The submitted clinical data from published literature was reviewed. [redacted] he studies were conducted in different patient populations (e.g., healthy volunteers, patients with various rheumatologic diseases). These subjects have normal adrenal gland reserve at baseline, and stimulated cortisol values above already normal values at baseline do not provide any information on [redacted]. The published studies also used different corticotrophin formulations [redacted] In addition, the other multiple deficiencies (the published studies unlikely meet the standards for "adequate and well-controlled" studies as described in 21 CFR 314.126; lack of consistency for the endpoint variable used in efficacy assessment across the studies and the timing of endpoint assessments; lack of uniformity in the cortisol assays used in efficacy analyses, etc.) make the results uninterpretable to draw conclusions [redacted]

(b) (4)

Overall, the team concluded that (b) (4)

(b) (4)

The drug (b) (4) as demonstrated in the submitted Study CA28049, it produces a delayed peak of cortisol levels (TE_{max} approximately of 6-8 hours). (b) (4)

(b) (4)

(b) (4)

reflected in the proposed label that does not provide instructions on safe and effective use of the product for this indication. The Applicant acknowledged the Division's concerns and agreed to voluntarily withdraw the indication for "diagnostic testing of adrenocortical function" from the proposed labeling.

8.1.2. Review of Published Data Submitted to provide additional evidence of the drug efficacy for the Indication (b) (4) (b) (4)

On June 29, 2021, the review team (b) (4) .

(b) (4) the submitted published literature and indicated that the information provided by the Sponsor, which included 3 published literature studies[8, 9, 10], (b) (4) (b) (4)

The reviewers therefore disagreed with the Applicant's rationale (b) (4)

(b) (4) recommended that the Applicant (b) (4) The Applicant agreed with the

(b) (4)

Agency's conclusions [redacted] (b) (4)

8.1.3. Review of Published Data Submitted to Support Efficacy of the Drug for the Indication "Acute exacerbation of multiple sclerosis (MS)"

DGE consulted the Division of Neurology 2 (DN2) on multiple occasions for recommendations on proposed labeling updates for Purified Cortrophin Gel regarding multiple sclerosis (MS) indication.

In their assessment (see Consult reviews in DARRTS, dated November 20, 2020 and September 14, 2021), DN2 reviewers concluded that, although infrequent, ACTH formulations, including H.P. Acthar Gel, continue to be utilized in clinical practice for treatment of acute MS relapse, and because the addition of this indication was done via a labeling supplement following a DESI review labeling supplement, DN2 considered it was reasonable for this indication to remain in the labeling for this product. Additionally, DN2 noted that the language utilized in the sponsor's proposed labeling was largely consistent with that of H.P. Acthar gel, which is currently marketed for acute exacerbations of MS and other indications. DN2 advised that the labeling for acute MS exacerbations be aligned between H.P. Acthar gel and this product for consistency and because the majority of the basis for their presumed efficacies are essentially the same, that is, collective clinical experience and historical literature.

8.1.4. Integrated Assessment of Effectiveness

Overall, no new clinical data were submitted to support the proposed indications in the label. The drug was found to be effective in all proposed indications during the DESI review in 1971.
[redacted] (b) (4)

8.2. Review of Safety

There are no new safety clinical data in this supplement other than those recorded in the PK/PD single dose study CA28049 conducted in 20 healthy volunteers.
There were no deaths, serious adverse events (SAEs), or subject discontinuations due to AEs in this study. Overall, a total of 14 treatment-emergent adverse events (TEAEs) were reported by 8 (40%) subjects during the study. The most common AE reported was injection site pain, which was reported by 6 (30%) subjects. All other AEs were reported by only 1 (5%) subject each. Of the 14 TEAEs reported, 11 were mild in severity and 3 were moderate. There were no notable trends identified in laboratory, vital sign, or ECG data in this study.

8.2.1. Integrated Assessment of Safety

The Applicant provided adequate CMC information that the to-be-marketed product and legacy product are comparable. As such, no new safety signals are expected with the re-introduction

of Purified Cosyntropin Gel to the market. The expected and already labeled adverse reactions are mostly due to the drug's mechanism of action (increased cortisol levels that may induce hypertension, hyperglycemia, growth delay, etc.), are monitorable and appropriately mitigated through the labeling.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not needed for this application.

10 Pediatrics

Not applicable. This application does not trigger PREA.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Refer to the complete labeling in the approval letter.

The proposed carton labeling, and prescribing information was found to be acceptable from a medication error perspective by DMEPA reviewer (refer to the review in DARRTS from August 9, 2021).

The following recommendations were communicated to and were addressed by Applicant:

Indication and Usage
The indications (b) (4)
doting this review cycle.

Clinical Pharmacology Section (Clinical Pharmacology recommendations)
Note: Red font represents new labeling language proposed by the reviewer.

> *Purified Cortrophin Gel is the anterior pituitary hormone which stimulates the functioning adrenal cortex to produce and secrete adrenocortical hormones*
> *Following administration of a single intramuscular injection of 80 Units of Cortrophin gel to healthy volunteers (n=20) in a open label PD study, the median time (range) to reach peak cortisol concentration was 8 (3-12) hours. Maximum (CV%) cortisol levels were 34.52 µg/dL (28.2%).*

Warnings
Immunogenicity Potential
The Applicant edited a statement "Purified Cortrophin Gel, (b) (4) (b) (4) is immunogenic" and removed (b) (4)" from the label. The product is a peptide (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

13 Postmarketing Requirements and Commitment

Not required

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARINA ZEMSKOVA
10/28/2021 12:20:55 PM

NAOMI N LOWY
10/28/2021 01:54:22 PM

Division of Gastroenterology (DG) Consult Memo

Application: NDA 008975/S-08
Drug: Purified Cortrophin Gel (repository corticotrophin injection, USP)
To: Dana Smith, Regulatory Health Project Manager, Division of General Endocrinology (DGE)
From: Anna Reed, MD, MPH, Medical Officer, Division of Gastroenterology (DG)
Matthew Kowalik, MD, Clinical Team Leader, DG
Through: Joette Meyer, PharmD, Associate Director of Labeling, DG; Juli Tomaino, MD, MS, Deputy Director, DG
Date Requested: June 29, 2021
Due Date Requested: October 1, 2021
Date Finalized: October 4, 2021
Reason for Consultation: Comment on the labeling indication of Cortrophin Gel (b) (4) (b) (4)

INTRODUCTION:
The Division of General Endocrinology (DGE) requested the Division of Gastroenterology (DG) to comment on (b) (4)

REGULATORY HISTORY:
Purified Cortrophin Gel (NDA 008975) was approved in the 1950s along with multiple adrenocorticotropic hormone products, including another repository corticotrophin product (H.P. Acthar Gel; NDA 008372), for the treatment of a wide range of disorders (e.g., rheumatologic disease, respiratory disorders, allergic and dermatologic states) that at the time were thought to benefit from steroid-mediated immunosuppression. H.P. Acthar Gel was approved in 1971 and updated in 1977 under the Drug Efficacy Study Implementation (DESI) (b) (4) (b) (4) However, at the time of a labeling update for H.P. Acthar Gel that added a new indication (infantile spasms) in 2010, a new NDA was created (NDA 022432) and the label was converted to the Physician Labeling Rule (PLR) format. (b) (4) .

Marketing of Purified Cortrophin Gel under NDA 008975 was discontinued in 1985 by the Applicant at the time. On June 29, 2021 the current Applicant submitted a CMC supplement for NDA 008975 that provides quality information and supporting data for reintroduction of the product in the US market. The Applicant has proposed (b) (4) .

DGE requested comments and recommendations from DG regarding the Applicant's proposal to (b) (4). An information request was sent to the Applicant on August 10, 2021 (b) (4) and requested additional data (b) (4) The Applicant submitted their response to the IR on August 20, 2021, which is the subject of this consult memo.

PRODUCT INFORMATION:
Purified Cortrophin Gel is a repository formulation of corticotropin for intramuscular (IM) or subcutaneous (SC) administration that is reported to bind to melanocortin receptors, which may play a role in immune cell-mediated anti-inflammatory effects, and inhibition of B-cell proliferation in a glucocorticoid-independent manner. The Applicant states that (b) (4) [redacted] ".

BACKGROUND OF ULCERATIVE COLITIS:
Ulcerative colitis (UC) is a multifactorial, immune-mediated, chronic inflammatory condition of the colonic mucosa affecting children and adults, with peak incidence in young adulthood. UC is a type of inflammatory bowel disease (IBD) that is characterized by recurring episodes of inflammation frequently manifesting as diarrhea with or without blood, urgency, tenesmus, and incontinence. Patients with involvement isolated to the distal colon may present with constipation accompanied by discharge of blood and mucous.

The severity of disease ranges from mild to severe, defined by frequency of bowel movements, presence or absence of blood, and other systemic symptoms (e.g., fever, fatigue, weight loss, anemia). Disease severity and response to therapy are assessed by monitoring clinical symptoms, endoscopy, imaging, and laboratory values. Approximately 15% of patients experience a severe course, with 20% of this population requiring hospitalization. Complications of acute severe UC include severe blood loss including hemorrhage, fulminant colitis and toxic megacolon, and perforation. Chronic disease can result in strictures, dysplasia, and colorectal cancer. Patients with UC have a slightly higher mortality compared to the general population and it is highest in the first year after diagnosis. Medical management and early colectomy for treatment non-responders have contributed to a sharp decline in morality. Additionally, up to twenty-five percent of patients have extra-intestinal manifestations of UC, which can include numerous organ systems and can contribute to significant extra-intestinal morbidity.

Diagnosis
The diagnosis of UC is made by a combination of clinical signs and symptoms along with endoscopic and histologic evidence of the disease. The diagnosis of UC requires biopsies of the colon obtained on endoscopy.

Treatment
Treatment for UC is determined based on the extent and severity of disease. Patients who present with proctitis frequently improve with topical therapy while those who present with extensive disease require systemic treatment and have a higher risk of disease-related morbidity (e.g., hospitalization, severe colitis, and colectomy).

Therapies approved for the treatment of mild to moderate UC include oral and topical 5-aminosalycilates (5-ASA), topical rectal corticosteroids, and oral budesonide. Approved therapies for the treatment for moderate to severe UC includes systemic corticosteroids, tumor necrosis factor (TNF)-α antagonists (e.g., infliximab, adalimumab, and golimumab), anti-integrins (e.g., vedolizumab and natalizumab), IL-12/IL-23 inhibitor (i.e., ustekinumab), Janus kinase inhibitors (i.e., tofacitinib), sphingosine 1-phosphate receptor modulators (i.e., ozanimod). In addition, immunomodulators (e.g., thiopurines, methotrexate, cyclosporine) are frequently used off-label.

For adult patients with UC, the American Gastroenterological Association (AGA) Guidelines are considered to guide the standard of care approach to treatment. These guidelines were most recently updated in 2019[1] and 2020[2] for mild to moderate UC and moderate to severe UC, respectively. The goal of therapy is to achieve remission and subsequently to maintain remission long-term to prevent recurrence of symptoms and inflammation of the colonic mucosa.

The AGA guidelines for the management of adult patients with extensive mild to moderate UC recommend treatment with a standard dose mesalamine (a 5-ASA) or diazo-bonded 5-ASA for induction and maintenance of remission.[3] Rectal mesalamine may be added for induction of remission in patients with suboptimal response or in patients with moderate disease activity.

The AGA guidelines for adult outpatients with moderate to severe UC recommends the use of infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab. Additionally, if a patient is a primary or secondary TNF-α antagonist non-responder, that is they either did not improve with a TNF-α antagonist or the effect wore off over time despite increasing dose and frequency, the guidelines recommend using ustekinumab or tofacitinib.

For hospitalized patients with severe disease, AGA guidelines suggest a three-to-five-day trial of intravenous (IV) corticosteroids to induce remission and decrease the risk of colectomy. If remission is induced, patients undergo a multi-week taper as a bridge to maintenance therapy, preferably a biologic agent, with or without thiopurine. For patients who are refractory to IV steroids, infliximab or cyclosporine are recommended.

(b) (4)

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QUESTIONS FOR DG REGARDING CURRENT SUBMISSION:
DGE requests recommendations or comments from DG regarding the indication (b) (4)

(b) (4)

(b) (4)

DG RESPONSE:
The Applicant was asked to provide (b) (4)

(b) (4)

The Applicant provides information (b) (4)

(b) (4)

(b) (4)

position. Importantly, two of the cited studies are from the 1950's and the last is from 1983. These studies pre-date modern therapies and current standard of care. Additionally, the term "remission" has a variable definition in each study and does not reflect the modern standardized definition of remission, including lack of consistent endoscopic assessment to evaluate the drug's effect on the colonic mucosa. Thus, in the following paragraphs, the term "remission" reflects the authors' definition in the cited article, which is not aligned the Division's currently recommended approach to defining clinical remission.

The first study (b) (4) [4] was a prospective, randomized, double blind clinical trial of IV corticotropin versus IV hydrocortisone in the treatment of severe UC for the duration of ten days. A higher proportion of steroid-naive patients who received corticotropin achieved "therapeutic success", or remission, (defined by the authors as "absence of all symptoms and the reduction of the frequency of bowel movements to two or less per day") at the end of the ten-day period compared to steroid-naïve patients who received hydrocortisone. In contrast, a higher proportion of patients with prior steroid exposure who received hydrocortisone were in remission compared to patients with prior steroid exposure who received corticotrophin. In this study, patients who were steroid-naïve had a higher proportion of remission following corticotropin compared to hydrocortisone but patients with prior steroid use had a *lower* proportion of remission following corticotropin compared to hydrocortisone. It is anticipated that most UC patients that might require an additional therapy will have previously received steroids. (b) (4) , Purified Cortrophin Gel is a repository formulation (made with gelatin for prolonged activity) used for IM or SC administration and IV administration is contraindicated; (b) (4)

The second study (b) (4) [5] was a multicenter clinical trial that compared the effects of daily corticotropin-gel versus daily oral cortisone administered to two groups of hospitalized patients with a "frank attack" (no definition was provided in the article) of UC initial presentation and relapse. Results showed that 60.7% patients in the corticotropin group achieved clinical remission (defined by "one or two stools a day without blood, no fever, no tachycardia, hemoglobin normal or returning to normal, ESR normal, gaining weight") at the end of the 6-week induction therapy compared to 38.8% in the cortisone group. There are several issues with these results. Although corticotropin therapy seemed to improve clinical symptoms in a larger proportion of patients in the induction period, this was only statistically significant when both initial and relapsing patient groups were combined, suggesting multiplicity. As shown in Table III of the publication, the result is not statistically significant when each group is assessed separately. Additionally, only about two-thirds of the patients had repeat sigmoidoscopy at the end of the six-week period, as this decision to repeat endoscopy was due to physician discretion. Thus, the data are incomplete and may be subject to bias because of the study design. Patients who met the definition of clinical remission were then enrolled in the subsequent part of the study evaluating oral corticoid versus inert tablet for remission

(b) (4)

maintenance for one year. Maintenance of remission was defined by lack of clinical symptoms and only a subset of patients underwent repeat sigmoidoscopy, again at physician discretion. The rate of complications was higher in that year in patients who were initially treated with corticotropin during induction. The study authors concluded that "this beneficial effect {of larger proportion of corticotropin-induced remission} is largely offset by the increased relapse rate during the succeeding year…The use of corticotrophin in the doses employed in the present study carries the price of a higher risk of complications due to therapy…"

The intent of the third study (b) (4)[6] was "an effort to provide a baseline for the natural history of ulcerative colitis as seen within the relatively stable confines of a single medical institution.." (i.e., Beth Israel Hospital). A retrospective review of the clinical course of 245 patients treated between 1930 and 1950 identified 52 patients with UC who were started on either corticortropin or steroids due to failure of "conservative treatment" of the time, that is "diet, rest, sedation, transfusions, antibiotics, and superficial psychotherapy" as well as sulfonamides. Upon the global chart review, the authors noted improvement in many of the severely ill UC patients after receipt of corticotropin and steroids, and thus they "attempted to assay the role of corticotropin and corticosteroids…not only in securing a remission but in altering, if possible, the natural course of the disease." The group of the 52 identified patients was treated over 6 years receiving a total of 81 courses of either corticotropin (via IM or IV), cortisone, or prednisone More patients on corticotropin had a "favorable response" (defined as "a drop in tachycardia and toxic appearance within 1-2 days, an increase in appetite and sense of well-being within 2-3 days, disappearance of blood from the stools within 3-5 days, decrease in abdominal cramps and number of bowel movements within 4-7 days, and an improved consistency of stools within 6-10 days"), compared to cortisone or prednisone in the acute period. Data regarding the proportion of patients undergoing endoscopy before or after treatment were not included. The authors briefly discussed that the available proctoscopy data showed a lag-time in improvement (i.e., there was not improvement, despite improved clinical symptomatology). Some patients were chosen to continue maintenance therapy with steroids for variable periods of time, but there were no uniform criteria to select these individuals. The relapse rate, again assessed at variable times, was similar in patients having received corticotropin and steroids in the acute phase.

There were numerous limitations with this study. First, it was a retrospective, observational study with the initial goal of understanding the natural course of UC, and thus has all of the limitations associated with the nature of retrospective reviews, including lack of randomization, methods to control/minimize bias, etc. Given that the data collection was limited to one hospital, this sample may not be representative of the larger population, especially given the lack of description baseline patient characteristics. The study results echo those of the (b) (4) (b) (4) article in that a greater proportion of patients on IV or IM corticotropin experienced symptom control early in a UC flare when compared to oral steroids; similarly to the (b) (4) conclusion, this did not alter relapse rates. Importantly, it was not clear what proportion of patients who achieved "favorable response" also underwent endoscopic assessment to determine whether the underlying inflammation has improved, and those who did, only underwent proctoscopy at unspecified and nonuniform timepoints. (b) (4) .

(b) (4)

At the time these studies were conducted , the available therapies and morbidity and mortality associated with UC were very different than in current practice. Steroids and 5-ASA have been used for several decades (sulfonamides were discovered in 1938, while steroids came to use in inflammatory bowel disease in the 1950's), and the first biologic agent, infliximab, was approved in 1998. Other biologic agents have been approved since that time, as evidenced by the previous discussion of available therapies, and have greatly improved the treatment options to induce and maintain remission. In addition, the disease was fatal for 30-40% of those afflicted in the 1950's.[7] While in the pre-biologic era approximately 50% of patients with UC ultimately required colectomy, the most recent data shows this number is approximately 15%. Deaths were reported in the literature provided by the applicant in both steroid and corticotropin groups. Currently, patients with UC have the same or slightly higher overall mortality compared with the general population, depending on source.[8,9]

Current treatment guidelines recommend biologic agents as the treatment of choice for patients who have failed or are refractory to steroids and these therapies are highly effective. Most of these therapies were approved based on long-term studies that assessed the effect of therapy on the relevant signs and symptoms and endoscopic appearance of the mucosa. (b) (4)

In conclusion, DG does not agree with the Applicant's rationale (b) (4)

(b) (4)

(b) (4)

(b) (4)

RECOMMENDED COMMENT TO THE APPLICANT:

We do not agree with your rationale (b) (4)

(b) (4)

Therefore, we do not agree (b) (4)

(b) (4)

(b) (4)

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/s/

ANNA W REED
10/04/2021 02:54:58 PM

MATTHEW R KOWALIK
10/04/2021 02:57:09 PM

JULI A TOMAINO
10/04/2021 03:04:49 PM

JOETTE M MEYER
10/04/2021 03:35:07 PM

Consult Memo
Division of Neurology 2

Date:	September 14, 2021
To:	Dana Smith Regulatory Health Project Manager Division of General Endocrinology (DGE) Center for Drug Evaluation and Research Geanina Roman-Popoveniuc, MD Clinical Reviewer Division of General Endocrinology (DGE) Center for Drug Evaluation and Research
From:	Laura E. Baldassari, MD, MHS Clinical Reviewer Division of Neurology 2, Office of Neuroscience Center for Drug Evaluation and Research
Through:	Paul R. Lee, MD, PhD Deputy Director Division of Neurology 2, Office of Neuroscience Center for Drug Evaluation and Research
Subject:	Consultation Memo
Application:	NDA 008975
Applicant/Sponsor:	ANI Pharmaceuticals, Inc.
Drug Product:	Repository corticotropin injection (Purified Cortrophin Gel)
Date of Request:	July 6, 2021

Consult Request

The Division of General Endocrinology (DGE) in the Center for Drug Evaluation and Research has requested a consultation from the Division of Neurology 2 (DN2) for recommendations regarding proposed labeling updates for Purified Cortrophin Gel. DGE received a prior approval supplement with Chemistry Manufacturing and Controls (CMC) data and labeling changes. The consult request stated that DGE “wanted to

make [DN2] aware of this supplement submission so that [DN2] may provide your recommendations or comments."

Regulatory History

Please refer to the previous DN2 consultation memorandum dated 11/20/2020 for pertinent regulatory history.

Clinical Background

Please refer to the previous DN2 consultation memorandum dated 11/20/2020 for pertinent clinical background regarding the treatment of multiple sclerosis (MS) exacerbations/relapses with repository corticotrophin products.

The following Information Request was sent to the sponsor on 8/10/21: "Please provide information to support that use of your product for exacerbation of multiple sclerosis indication is consistent with current clinical practice."

The sponsor replied on 8/17/21, and submitted a summary of available claims data, medical literature, and ongoing clinical trials related to ACTH use for acute relapses (exacerbations) of MS. Though this information is not adequate to confirm or establish substantial evidence of effectiveness, it provides reasonable indication that ACTH continues to be utilized in clinical practice, albeit rarely, for the treatment of acute relapses of MS. The sponsor also indicates that ACTH is mentioned on UpToDate, by the National MS Society, and in a continuing education program by the Cleveland Clinic as a potential treatment for acute MS relapse.

> ***Reviewer comment:*** *Though it appears to be rarely utilized in this setting, current clinical practice appears to include ACTH as a potential option for treatment of acute MS relapse. HP Acthar gel, a complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides, is approved to treat acute MS exacerbations.*

Proposed Labeling

The sponsor proposes the following MS- and selected safety-related language in revised labelling. DN2 suggestions for revision are included in red.

Indication

Purified Cortrophin Gel may be employed in the following disorders:

9. Nervous System: Acute exacerbations of multiple sclerosis.

Precautions: General

Although controlled clinical trials have shown ACTH to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that it affects the ultimate outcome or natural history of the disease. (b) (4)

> ***Reviewer comment:*** *We propose deletion of this sentence, as it is not included in HP Acthar Gel labeling, and implies* (b) (4) *" based on data that have not been reviewed by the Division.*

Relative adrenocortical insufficiency induced by prolonged corticotropin therapy may be minimized by gradual reduction of corticotropin dosage. This type of insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress during that period, hormone therapy should be reinstituted.

The lowest possible dosage of corticotropin should be used to control the condition under treatment, and when reduction in dosage is possible the reduction should be gradual.

Since complications of treatment with ACTH are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment.

Dosage and Administration

In the treatment of acute exacerbations of multiple sclerosis daily intramuscular doses of 80-120 units for 2-3 weeks.

Recommendations

The review of this supplement will be driven largely by the outcome of the CMC evaluation, which is related to the bridging of the modern cortrophin gel product to the originally approved product. This bridging is quite challenging given the lack of existence of any previously marketed product.

Since the sponsor is proposing changes to the previously approved labeling of the product, the Agency is obligated to review the proposed changes and the entirety of labeling for appropriateness of the claims and the adequacy of the findings supporting any labeling component. This consultation memorandum focuses on the indication for acute exacerbations of MS.

We have identified no obvious new safety concerns with the inclusion of the multiple sclerosis acute exacerbation indication for this product.

Overall, it appears that while infrequent, ACTH continues to be utilized in clinical practice for treatment of acute MS relapse. Given the addition of this indication via labeling supplement circa 1977 or 1978 (following a DESI review), it is reasonable for this indication to remain in the labeling for this product. Additionally, the language utilized in the sponsor's proposed labeling is largely consistent with that of H.P. Acthar gel, which is currently marketed for acute exacerbations of MS and other indications. We advise that the labeling for acute MS exacerbations be aligned between HP Acthar gel and this product for consistency and because the majority of the basis for their presumed efficacies are essentially the same, that is, collective clinical experience and historical literature.

Laura Baldassari, MD, MHS
Clinical Reviewer
Division of Neurology 2, Office of Neuroscience
Center for Drug Evaluation and Research

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/s/

LAURA E BALDASSARI
09/14/2021 04:11:31 PM

PAUL R LEE
09/14/2021 04:12:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

008975Orig1s008

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 31, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 008975/S-008
Product Name and Strength:	Purified Cortrophin Gel (repository corticotrophin injection USP) 400 units/5 mL, (80 units/mL)
Applicant/Sponsor Name:	Ani Pharmaceuticals, Inc
OSE RCM #:	2021-1353-1
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD, RPh
DMEPA 1 Team Leader:	Sevan H. Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container labels received on August 17, 2021 for Purified Cortrophin Gel. Division of General Endocrinology (DGE) requested that we review the revised container label for Purified Cortrophin Gel (repository corticotrophin injection USP) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

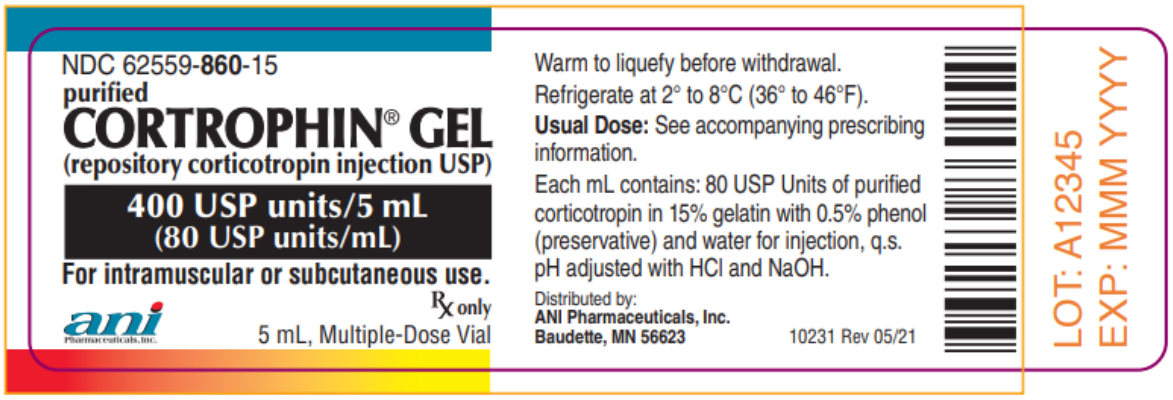
2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Howard, C. Label and Labeling Review for Purified Cortrophin Gel (NDA 008975/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 Aug 09. RCM No.: 2021-1353.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 17, 2021

Container labels



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/s/

CORWIN D HOWARD
08/31/2021 01:29:16 PM

SEVAN H KOLEJIAN
08/31/2021 02:24:01 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 9, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 008975/S-008
Product Name, Dosage Form, and Strength:	Purified Cortrophin Gel (repository corticotrophin injection USP) , 40 units/mL and 80 units/mL.
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Ani Pharmaceuticals, Inc
FDA Received Date:	June 29, 2021
OSE RCM #:	2021-1353
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD, RPh
DMEPA 1 Team Leader:	Sevan H. Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

Ani Pharmaceuticals, Inc. resubmitted a Manufacturing prior approval supplement (PAS) for Purified Cortrophin Gel (repository corticotrophin injection USP) on June 29, 2021. Subsequently, the Division of General Endocrinology (DGE) requested that we review the proposed label and labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Ani Pharmaceuticals, Inc. submitted a Manufacturing (CMC) prior approval supplement (PAS) for Purified Cortrophin Gel (repository corticotrophin injection USP) on March 23, 2020. The Division of General Endocrinology (DGE) subsequently sent a Refuse to File (RTF) communication to Ani Pharmaceuticals, Inc. on April 27, 2020.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed container label, carton labeling, and prescribing information (PI) for Purified Cortrophin Gel (repository corticotrophin injection USP) Our evaluation of the proposed PI and carton labeling did not identify areas of vulnerability that may lead to medication errors. However, we note that the container label does not note the expiration date and we made a recommendation to add.

4 CONCLUSION & RECOMMENDATIONS

The proposed carton labeling, and prescribing information (PI) for Purified Cortrophin Gel (repository corticotrophin injection USP) is acceptable from a medication error perspective. We have no further recommendations at this time. However, we note that the container label can be improved and provided our recommendations below in Section 4.1.

4.1 RECOMMENDATIONS FOR ANI PHARMACEUTICALS, INC

We recommend the following be implemented prior to approval of this NDA Supplement:

A. Container Labels

1. As currently presented, the container label lacks the expiration date. Add the expiration date on container label per 21 CFR 201.7.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Purified Cortrophin Gel (repository corticotrophin injection USP) received on June 29, 2021, from Ani Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Purified Cortrophin Gel (repository corticotrophin injection USP)	
Initial Approval Date	June 16, 1954
Active Ingredient	repository corticotrophin
Indication	1. 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. Acute gouty arthritis. 2. Collagen diseases: During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus. Systemic dermatomyositis (polymyositis). 3. Dermatologic diseases: Severe erythema multiforme (Stevens-Johnson syndrome). Severe psoriasis. 4. Allergic states: (b) (4) Atopic dermatitis. Serum sickness. 5. Ophthalmic diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: Allergic conjunctivitis. Keratitis. Iritis and iridocyclitis. Diffuse posterior uveitis and choroiditis. Optic neuritis. Chorioretinitis. Anterior segment inflammation. 6. Respiratory diseases: Symptomatic sarcoidosis.

	7. Edematous states: 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. (b) (4) 9. Nervous system: Acute exacerbations of multiple sclerosis.
Route of Administration	For intramuscular or subcutaneous use.
Dosage Form	Injection
Strength	40 units/mL and 80 units/mL.
Dose and Frequency	Standard tests for verification of adrenal responsiveness to corticotropin may utilize as much as 80 units as a single injection or one or more injections of a lesser dosage. Verification tests should be performed prior to treatment with corticotropins. The test should utilize the route(s) of administration proposed for treatment. Following verification 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, plasma and urine corticosteroid levels and the initial response of the patient. Only gradual change in dosage schedules should be attempted, after full drug effects have become apparent. In the treatment of acute exacerbations of multiple sclerosis daily intramuscular doses of 80-120 units for 2-3 weeks. The chronic administration of more than 40 units daily may be associated with uncontrollable adverse effects. When reduction in dosage is indicated this should be accomplished gradually by either reducing the amount of each injection, or administering injections at longer intervals, or by a combination of both of the above. During reduction of dosage, careful consideration should be given to the disease being treated, the general medical condition of the patient and the duration over which corticotropin was administered. This product may be administered subcutaneously or intramuscularly. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

How Supplied	Purified Cortrophin Gel (repository corticotrophin injection USP) is available in a potency of 80 USP units/mL: 5 mL multiple-dose vials (NDC 62559-860-15)
Storage	Refrigerate at 2° to 8°C (36° to 46°F). Warm to liquefy before withdrawal.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 3, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, “008975” and “repository corticotropin“. Our search did not identify any relevant reviews.

APPENDIX G. LABELS AND LABELING

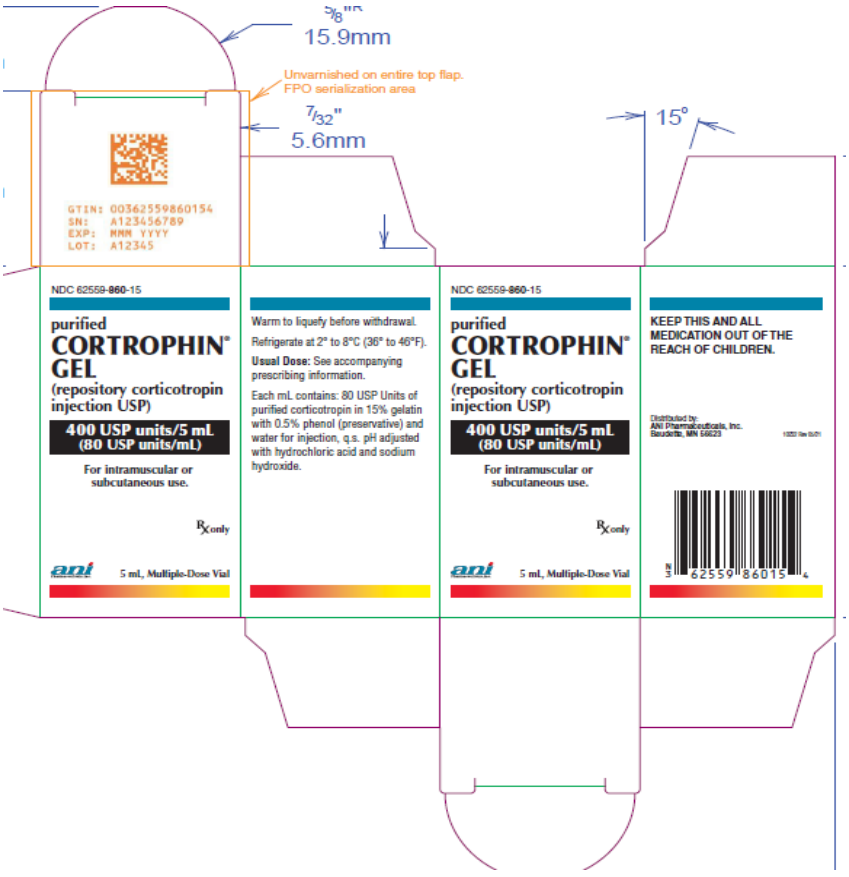
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Purified Cortrophin Gel (repository corticotrophin injection USP) labels and labeling submitted by Ani Pharmaceuticals, Inc.

- Container label received on June 29, 2021
- Carton labeling received on June 29, 2021
- Prescribing Information (Image not shown) received on June 29, 2021, available from \\CDSESUB1\evsprod\NDA008975\0031

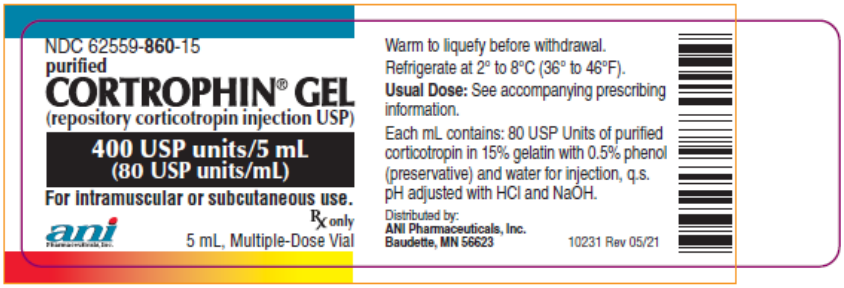
G.2 Label and Labeling Images

Carton Labeling



[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Container Label



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SEVAN H KOLEJIAN
08/09/2021 03:36:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

008975Orig1s008

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

Smith, Dana

From: Smith, Dana
Sent: Wednesday, September 29, 2021 10:58 AM
To: Connolly, Ellen
Subject: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP) 40 units/mL and 80 units/mL
Attachments: NDA 008975_draft_insert_word_06.29.21_NEG1_.docx

Dear Ms. Connolly,

In regard to NDA 008975/ repository corticotrophin injection 40 units/mL and 80 units/mL, received July 29, 2021, please see the 1st round of FDA comments on the draft package insert (see attached Word document). We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration.

Please accept all FDA edits with which you agree. The document that you return to us should only show in tracked changes: (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "ANI Pharmaceuticals response to FDA change" or "ANI Pharmaceuticals comment."

We ask that you provide the revised labeling **as soon as possible or by October 5, 2021**. You can return the updated package insert via email as the updated versions need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3385
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/s/

DANA M SMITH
10/27/2021 03:09:41 PM

Smith, Dana

From: Smith, Dana
Sent: Wednesday, October 27, 2021 8:33 AM
To: Connolly, Ellen
Subject: RE: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP) 40 units/mL and 80 units/mL

Dear Ms. Connolly,

In regard to NDA 008975/ repository corticotrophin injection 40 units/mL and 80 units/mL, received July 29, 2021, we have no further comments on the labeling submitted on October 25, 2021, via email.

Please submit a final clean version of the combined labeling (PI/IFU) to the sNDA **as soon as possible or by October 28, 2021**.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology
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19 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DANA M SMITH
10/27/2021 03:09:41 PM

Smith, Dana

From: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Sent: Wednesday, October 27, 2021 11:29 AM
To: Smith, Dana
Subject: [EXTERNAL] RE: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP)/ Information Request

Hi Dana,

We can certainly provide this by COB. Would it be acceptable to submit this statement in the same submission as the labeling documents just requested?

Ellen Connolly
Vice President, Regulatory Affairs
ANI Pharmaceuticals, Inc.
Office : 919.647.9793
Cell: (b) (6)
Fax : 888.519.0459
www.anipharmaceuticals.com

From: Smith, Dana <Dana.Smith@fda.hhs.gov>
Sent: Wednesday, October 27, 2021 11:27 AM
To: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Subject: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP)/ Information Request

Dear Ms. Connolly,

Please provide an environmental assessment or categorical exclusion statement for the reintroduction of the product.

Please provide by **COB today**.

Please confirm receipt.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3385
10903 New Hampshire Avenue
Silver Spring, MD 20903

dana.smith@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

DANA M SMITH
10/27/2021 03:25:15 PM

Smith, Dana

From: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Sent: Wednesday, October 20, 2021 3:11 PM
To: Smith, Dana
Subject: [EXTERNAL] RE: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP)/Information Request

Hi Dana
I am confirming receipt and will let you know if we have any questions.

Ellen Connolly
Vice President, Regulatory Affairs
ANI Pharmaceuticals, Inc.
Office : 919.647.9793
Cell: (b) (6)
Fax : 888.519.0459
www.anipharmaceuticals.com

From: Smith, Dana <Dana.Smith@fda.hhs.gov>
Sent: Wednesday, October 20, 2021 2:44 PM
To: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Subject: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP)/Information Request

Dear Ms. Connolly,

Please refer to your New Drug Application(NDA) for 008975,prior approval supplement, received June 29, 2021, for purified Cortrophin Gel (repository corticotrophin injection USP). We have the following requests:

(b) (4)

(b) (4)

Please provide your response by COB **Friday, October 22nd.**

Please **confirm** receipt and let me know if you have any questions.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3385
10903 New Hampshire Avenue
Silver Spring, MD 20903
dana.smith@fda.hhs.gov

(b) (4)

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/s/

DANA M SMITH
10/20/2021 04:55:59 PM

Smith, Dana

From: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Sent: Friday, October 1, 2021 3:27 PM
To: Smith, Dana
Subject: [EXTERNAL] RE: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP)/Information Request

Good Afternoon Dana,

I am confirming receipt

We will let you know if we have any questions

Have a nice weekend!

Ellen Connolly
Vice President, Regulatory Affairs
ANI Pharmaceuticals, Inc.
Office : 919.647.9793
Cell: (b) (6)
Fax : 888.519.0459
www.anipharmaceuticals.com

From: Smith, Dana <Dana.Smith@fda.hhs.gov>
Sent: Friday, October 1, 2021 3:08 PM
To: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Subject: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP)/Information Request

Dear Ms. Connolly,

Please refer to your New Drug Application(NDA) for 008975,prior approval supplement, received June 29, 2021, for purified Cortrophin Gel (repository corticotrophin injection USP). We have the following requests:

Immunogenicity Risk Assessment

1. Your immunogenicity risk assessment (Section 5.3.5.4) included testing for the activation of innate immune responses via an *in vitro* assay (Section 4.1.2 of Immunogenicity Risk Assessment). However, the report does not appear to be provided and there is limited information provided in the immunogenicity risk assessment summary to ultimately conclude on whether the approach and data are acceptable. Provide the report or indicate the location of the report in the supplement submission. As part of your response, ensure that you address the following comments:

    a. It is unclear what readout was used in the assessment. While it may be acceptable to include different types of assay readouts, it is expected that this assessment includes at least cytokine production from a panel of pro- and anti-inflammatory cytokines. The selection of cytokines should be broad, justified, and ensure a sensitive readout for the assay.

b. [redacted] Provide a risk assessment [redacted] You should clarify whether or not the manufacturing process and in-use conditions [redacted] impact the critical quality attributes of the product.

c. [redacted] concentration tested in the assay was [redacted] µg/mL. Clarify the range of concentrations [redacted] We recommend that the assay be performed with an undiluted sample or the highest possible serially diluted concentration that does not interfere with the assay response, because higher concentrations will have [redacted] may be more relevant to the concentration at the site of innate immune activation. Provide appropriate justification and data [redacted] used in the assay are relevant and do not impact the viability and metabolic activity of the cells present.

d. The information in the report should be detailed to understand the cell culture conditions.

Please provide your response by **12pm on Wednesday, October 6th.**

Please **confirm** receipt and let me know if you have any questions.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3385
10903 New Hampshire Avenue
Silver Spring, MD 20903
dana.smith@fda.hhs.gov

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/s/

DANA M SMITH
10/01/2021 03:48:13 PM

Smith, Dana

From: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Sent: Wednesday, September 22, 2021 2:40 PM
To: Smith, Dana
Subject: [EXTERNAL] RE: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP)/Information Request

Hi Dana

I am confirming receipt and thank you for providing the courtesy copy via email.

Kindly confirm that there is no specific due date assigned and that just a prompt response is expected.

We will review with the team in further detail, and if any more questions we will reach out.

Ellen Connolly
Vice President, Regulatory Affairs
ANI Pharmaceuticals, Inc.
Office : 919.647.9793
Cell: (b) (6)
Fax : 888.519.0459
www.anipharmaceuticals.com

From: Smith, Dana <Dana.Smith@fda.hhs.gov>
Sent: Wednesday, September 22, 2021 2:29 PM
To: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Subject: NDA 008975/ purified Cortrophin Gel (repository corticotrophin injection USP)/Information Request

Dear Ms. Connolly,

I am forwarding you a PDF courtesy copy of the Information Request letter for NDA 008975. You will receive an official copy of this letter via US mail.

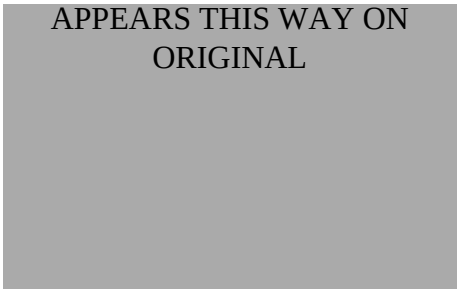
Please **confirm** receipt and let me know if you have any questions.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3385

10903 New Hampshire Avenue
Silver Spring, MD 20903
dana.smith@fda.hhs.gov



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/s/

DANA M SMITH
09/22/2021 05:05:19 PM

U.S. FOOD & DRUG ADMINISTRATION

NDA 008975/S-008

INFORMATION REQUEST

ANI Pharmaceuticals, Inc.
Attention: Ellen Connolly
Vice President, Regulatory Affairs
210 Main Street West
Baudette, MN 56623

Dear Ms. Connolly:

Please refer to your supplemental new drug application (sNDA) dated and received June 29, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Purified Cortrophin Gel (repository corticotrophin injection USP).

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your sNDA.

We have reviewed the information submitted, (b) (4) ."

As you are aware, (b) (4) (b) (4) (b) (4)

(b) (4) Your drug is (b) (4) as expected and demonstrated in the submitted Study CA 28049, it produces a delayed peak of cortisol levels (TE_{max} approximately of 6-8 hours). (b) (4)

(b) (4)

The published literature submitted in your sNDA and in responses to our information requests from August 4 and 10, 2021, (b) (4) n.

(b) (4)

If you have any questions, call Dana Smith, Regulatory Project Manager, at 240-402-9906.

Sincerely,

{See appended electronic signature page}

Theresa E. Kehoe, MD
Division Director
Division of General Endocrinology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

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/s/

THERESA E KEHOE
09/22/2021 02:21:10 PM

Smith, Dana

From: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Sent: Thursday, August 12, 2021 12:12 PM
To: Smith, Dana
Cc: Hamilton-Stokes, Deveonne
Subject: [EXTERNAL] RE: NDA 008975/Cortrophin (Repository Corticotrophin) /Container label(s)

Hi Dana
I am confirming receipt

Ellen Connolly
Vice President, Regulatory Affairs
ANI Pharmaceuticals, Inc.
Office : 919.647.9793
Cell: (b) (6)
Fax : 888.519.0459
www.anipharmaceuticals.com

From: Smith, Dana <Dana.Smith@fda.hhs.gov>
Sent: Thursday, August 12, 2021 12:02 PM
To: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Cc: Hamilton-Stokes, Deveonne <Deveonne.Hamilton-Stokes@fda.hhs.gov>
Subject: NDA 008975/Cortrophin (Repository Corticotrophin) /Container label(s)

Hello Ms. Connolly,

In regard to New Drug Application (NDA) for 008975,prior approval supplement, received June 29, 2021, for purified Cortrophin Gel (repository corticotrophin injection USP), please see the below issues we have identified with the submitted container label(s).

We recommend the following be implemented prior to approval of this NDA Supplement:

A. Container Labels

1. As currently presented, the container label lacks the expiration date. Add the expiration date on container label per 21 CFR 201.7.

We ask that you provide the revised container label(s) by **Friday, August 20, 2021**.

Please **confirm** receipt and let me know if you have any questions.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3385
10903 New Hampshire Avenue
Silver Spring, MD 20903
dana.smith@fda.hhs.gov

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DANA M SMITH
08/12/2021 01:34:14 PM

Smith, Dana

From: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Sent: Tuesday, August 10, 2021 8:50 PM
To: Smith, Dana
Subject: [EXTERNAL] RE: NDA 008975/Cortrophin (Repository Corticotrophin)/ Information request

Hi Dana
I am confirming receipt

Thank you!

Ellen Connolly
Vice President, Regulatory Affairs
ANI Pharmaceuticals, Inc.
Office : 919.647.9793
Cell: (b) (6)
Fax : 888.519.0459
www.anipharmaceuticals.com

From: Smith, Dana <Dana.Smith@fda.hhs.gov>
Sent: Tuesday, August 10, 2021 5:46 PM
To: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Subject: NDA 008975/Cortrophin (Repository Corticotrophin)/ Information request

Dear Ms. Connolly,

Please refer to your New Drug Application(NDA) for 008975,prior approval supplement, received June 29, 2021, for purified Cortrophin Gel (repository corticotrophin injection USP). We have the following requests:

(b) (4)

Please provide your response by **Friday, August 13, 2021.**

Please **confirm** receipt and let me know if you have any questions.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3385
10903 New Hampshire Avenue
Silver Spring, MD 20903
dana.smith@fda.hhs.gov

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/s/

DANA M SMITH
08/11/2021 07:30:11 AM

Smith, Dana

From: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Sent: Tuesday, August 10, 2021 3:26 PM
To: Smith, Dana
Subject: [EXTERNAL] Re: NDA 008975/Cortrophin (Repository Corticotrophin)/ Information request

Dana
I am confirming receipt

Ellen Connolly
Vice President, Regulatory Affairs
ANI Pharmaceuticals, Inc.
Office: 919.647.9793
Cell: (b) (6)
Fax: 888.519.0459
www.anipharmaceuticals.com

On Aug 10, 2021, at 2:40 PM, Smith, Dana <Dana.Smith@fda.hhs.gov> wrote:

Dear Ms. Connolly,

Please refer to your New Drug Application(NDA) for 008975,prior approval supplement, received June 29, 2021, for purified Cortrophin Gel (repository corticotrophin injection USP). We have the following requests:

- **Please provide information to support that use of your product for exacerbation of multiple sclerosis indication is consistent with current clinical practice.**

Please provide your response by **Friday, August 13, 2021.**

Please **confirm** receipt and let me know if you have any questions.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3385
10903 New Hampshire Avenue

Silver Spring, MD 20903
dana.smith@fda.hhs.gov

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/s/

DANA M SMITH
08/10/2021 03:53:50 PM

Smith, Dana

From: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Sent: Wednesday, August 4, 2021 10:32 PM
To: Smith, Dana
Subject: [EXTERNAL] RE: NDA 008975/Cortrophin (Repository Corticotrophin)/ Information request

Hi Dana

I am confirming receipt of this email/IR. I will let you know if we have any questions.

Thank you!

Ellen Connolly
Vice President, Regulatory Affairs
ANI Pharmaceuticals, Inc.
Office : 919.647.9793
Cell: (b) (6)
Fax : 888.519.0459
www.anipharmaceuticals.com

From: Smith, Dana <Dana.Smith@fda.hhs.gov>
Sent: Wednesday, August 4, 2021 5:45 PM
To: Connolly, Ellen <ellen.connolly@anipharmaceuticals.com>
Subject: NDA 008975/Cortrophin (Repository Corticotrophin)/ Information request

Dear Ms. Connolly,

Please refer to your New Drug Application(NDA) for 008975,prior approval supplement, received June 29, 2021, for purified Cortrophin Gel (repository corticotrophin injection USP). We have the following requests:

(b) (4)

Please provide your response by **Monday, August 9, 2021.**

Please **confirm** receipt and let me know if you have any questions.

Kind Regards,

Dana

Dana M. Smith
Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3385
10903 New Hampshire Avenue
Silver Spring, MD 20903
dana.smith@fda.hhs.gov

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/s/

DANA M SMITH
08/05/2021 07:19:34 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Immunology and Inflammation - Division of Gastroenterology (DG)

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Dana Smith
Regulatory Health Project Manager
On behalf of the Division of General Endocrinology (DGE)
Center for Drug Evaluation and Research
Dana.Smith@fda.hhs.gov
240-402-9906

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
07/29/2021	N/A	NDA 008975	Resubmission of Supplement(S-008)	June 29, 2021

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
purified Cortrophin Gel (repository corticotrophin injection USP)	standard	adrenocortical	10/1/2021

NAME OF FIRM: ANI Pharmaceuticals, Inc.'s

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Resubmission of Supplement(S-008)

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

We have received a prior approval supplement for NDA 008975/ Purified Cortrophin Gel (Repository Corticotrophin injection) from Ani Pharmaceuticals. In March 2018, we provided a written response to a Type C Meeting, which discuss ANI's proposed strategies for the studies and data required for the re-commercialization of Purified Cortrophin® Gel USP, 80 units/mL. There was a telecon in May 2018 as a follow-up to the meeting. A General Advice Letter was issued May 2018, which provided additional comments to consider for the re-commercialization effort of Purified Cortrophin® Gel USP. There were some concerns about demonstrating safety of the product but no clinical information was submitted. In March 2020, Ani submitted a new supplement (Supplement-8) and we issued a refuse to file letter with CMC comments. This supplement (resubmission of supplement-8) provides detailed CMC information. The applicant also made changes to the label.

We wanted to make you aware of this supplement submission so that you may provide your recommendations or comments (b) (4)

EDR Location: \\CDSESUB1\evsprod\NDA008975\0031

Timelines:
Receipt date: 06/29/2021
Tentative Reviews/labeling edits due from reviewers by: 08/10/2021 (let me know if you need additional time)
PDUFA goal date: 10/29/2021

Clinical reviewer & Team Leader: Geanina Roman-Popoveniuc /Marina Zemskova
CMC reviewer & Team Leader: Pallaiah Thammana/ Zedong Dong

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Dana Smith	☐ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

DANA M SMITH
07/29/2021 04:52:33 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Immunology and Inflammation - Division of Dermatology and Dentistry (DDD)

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Dana Smith
Regulatory Health Project Manager
On behalf of the Division of General Endocrinology (DGE)
Center for Drug Evaluation and Research
Dana.Smith@fda.hhs.gov
240-402-9906

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
07/29/2021	N/A	NDA 008975	Resubmission of Supplement(S-008)	June 29, 2021

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
purified Cortrophin Gel (repository corticotrophin injection USP)	standard	adrenocortical	10/1/2021

NAME OF FIRM: ANI Pharmaceuticals, Inc.'s

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Resubmission of Supplement(S-008)

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

We have received a prior approval supplement for NDA 008975/ Purified Cortrophin Gel (Repository Corticotrophin injection) from Ani Pharmaceuticals. In March 2018, we provided a written response to a Type C Meeting, which discuss ANI's proposed strategies for the studies and data required for the re-commercialization of Purified Cortrophin® Gel USP, 80 units/mL. There was a telecon in May 2018 as a follow-up to the meeting. A General Advice Letter was issued May 2018, which provided additional comments to consider for the re-commercialization effort of Purified Cortrophin® Gel USP. There were some concerns about demonstrating safety of the product but no clinical information was submitted. In March 2020, Ani submitted a new supplement (Supplement-8) and we issued a refuse to file letter with CMC comments. This supplement (resubmission of supplement-8) provides detailed CMC information. The applicant also made changes to the label.

We wanted to make you aware of this supplement submission so that you may provide your recommendations or comments about the indications (severe psoriasis and atopic dermatitis) listed in the label.

EDR Location: \\CDSESUB1\evsprod\NDA008975\0031

Timelines:
Receipt date: 06/29/2021
Tentative Reviews/labeling edits due from reviewers by: 08/10/2021 (let me know if you need additional time)
PDUFA goal date: 10/29/2021

Clinical reviewer & Team Leader: Geanina Roman-Popoveniuc /Marina Zemskova
CMC reviewer & Team Leader: Pallaiah Thammana/ Zedong Dong

SIGNATURE OF REQUESTOR Dana Smith	METHOD OF DELIVERY (Check all that apply) ☐ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

DANA M SMITH
07/29/2021 04:49:08 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Dana Smith Regulatory Health Project Manager On behalf of the Division of General Endocrinology (DGE) Center for Drug Evaluation and Research Dana.Smith@fda.hhs.gov 240-402-9906

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
7/13/2021	n/a	NDA 008975	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
purified Cortrophin Gel (repository corticotrophin injection USP)	standard	adrenocortical	10/01/2021

NAME OF FIRM:	
ANI Pharmaceuticals, Inc.'s	PDUFA Date: 10/29/2021

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PRESCRIBING INFORMATION (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☒ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission:

EDR Location: \\CDSESUB1\evsprod\NDA008975\0031

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:
We have received a prior approval supplement for NDA 008975/ Purified Cortrophin Gel (Repository Corticotrophin injection) from Ani Pharmaceuticals. In March 2018, we provided a written response to a Type C Meeting, which discuss ANI's proposed strategies for the studies and data required for the re-commercialization of Purified Cortrophin® Gel USP, 80 units/mL. There was a telecon in May 2018 as a follow-up to the meeting. A General Advice Letter was issued May 2018, which provided additional comments to consider for the re-commercialization effort of Purified Cortrophin® Gel USP. There were some concerns about demonstrating safety of the product, but no clinical information was submitted. In March 2020, Ani submitted a new supplement (Supplement-8) and we issued a refuse to file letter with CMC comments. This supplement provides detailed CMC information and changes to the label.
Previously Neurology was involved with the modern HP Acthar Gel label. We wanted to make you aware of this supplement submission so that you may provide your recommendations or comments.

Timelines:
Receipt date: 06/29/2021
Tentative Reviews/labeling edits due from reviewers by: 08/10/2021 (let me know if you need additional time)
Internal Meeting: 07/29/2021
PDUFA goal date: 10/29/2021

Clinical reviewer & Team Leader: Geanina Roman-Popoveniuc /Marina Zemskova
CMC reviewer & Team Leader: Pallaiah Thammana/ Zedong Dong

Mid-Cycle Meeting:
Labeling Meetings:
Wrap-Up Meeting:

SIGNATURE OF REQUESTER
Dana Smith

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

DANA M SMITH
07/16/2021 01:00:21 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM:
Dana Smith
Regulatory Health Project Manager
Division of General Endocrinology (DGE)
Center for Drug Evaluation and Research
Dana.Smith@fda.hhs.gov
240-402-9906

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 8, 2021	n/a	NDA 008975	Supplement	June 29, 2021

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
repository corticotropin injection, USP	standard	n/a	October 1, 2021

NAME OF FIRM: ANI Pharmaceuticals, Inc.'s

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☐ OTHER *(SPECIFY BELOW)*: Prior Approval Supplement

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We have received a prior approval supplement for NDA 008975/ Purified Cortrophin Gel (Repository Corticotrophin injection) from Ani Pharmaceuticals. In March 2018, we provided a written response to a Type C Meeting, which discuss ANI's proposed strategies for the studies and data required for the re-commercialization of Purified Cortrophin® Gel USP, 80 units/mL. There was a telecon in May 2018 as a follow-up to the meeting. A General Advice Letter was issued May 2018, which provided additional comments to consider for the re-commercialization effort of Purified Cortrophin® Gel USP. There were some concerns about demonstrating safety of the product but no clinical information was submitted. In March 2020, Ani submitted a new supplement (Supplement-8) and we issued a refuse to file letter with CMC comments.

This supplement provides detailed CMC information as well as changes to the label.
We wanted to make you aware of this supplement submission so that you may provide recommendations or comments if necessary.

The reviewers previously assigned to this NDA (for the meeting request) were Melina Fanari and her TL is Sevan Kolejian.

EDR Location: \\CDSESUB1\evsprod\NDA008975\0031

Timelines:
Receipt date: 06/29/2021
Tentative Reviews/labeling edits due from reviewers by: 08/10/2021 (let me know if you need additional time)
Internal Meeting: 07/29/2021
PDUFA goal date: 10/29/2021

Clinical reviewer & Team Leader: Geanina Roman-Popoveniuc /Marina Zemskova
CMC reviewer & Team Leader: Pallaiah Thammana/ Zedong Dong

SIGNATURE OF REQUESTER Dana Smith	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☐ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

DANA M SMITH
07/08/2021 04:15:46 PM

NDA 008975/S-008

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

ANI Pharmaceuticals, Inc.
Attention: Ellen Connolly
Vice President, Regulatory Affairs
210 Main Street West
Baudette, MN 56623

Dear Ms. Connolly:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) in response to our April 27, 2020, refusal to file letter for the following:

NDA NUMBER: 008975

SUPPLEMENT NUMBER: 008

PRODUCT NAME: purified Cortrophin Gel (repository corticotrophin injection USP)

DATE OF SUBMISSION: June 29, 2021

DATE OF RECEIPT: June 29, 2021

This supplemental application provides quality information and supporting data for reintroduction of the product in the US market.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 28, 2021, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be October 29, 2021.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

If you have questions, call me at (240) 402-9906.

Sincerely,

{See appended electronic signature page}

Dana Smith
Regulatory Project Manager
General Endocrinology
Division of Regulatory Operations for
Cardiology, Hematology, Endocrinology, and
Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

DANA M SMITH
07/06/2021 04:09:42 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Neurology

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Dana Smith, B.S.
Regulatory Health Project Manager
Division of General Endocrinology (DGE)
Center for Drug Evaluation and Research
Dana.Smith@fda.hhs.gov
240-402-9906

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
07/02/2021	n/a	NDA 008975	Supplement(S-009)	June 29, 2021

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
repository corticotropin injection, USP	standard	n/a	October 1, 2021

NAME OF FIRM: ANI Pharmaceuticals, Inc.'s

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: Supplement(S-009)

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

We have received a prior approval supplement for NDA 008975/ Purified Cortrophin Gel (Repository Corticotrophin injection) from Ani Pharmaceuticals. In March 2018, we provided a written response to a Type C Meeting, which discuss ANI's proposed strategies for the studies and data required for the re-commercialization of Purified Cortrophin® Gel USP, 80 units/mL. There was a telecon in May 2018 as a follow-up to the meeting. A General Advice Letter was issued May 2018, which provided additional comments to consider for the re-commercialization effort of Purified Cortrophin® Gel USP. There were some concerns about demonstrating safety of the product but no clinical information was submitted. In March 2020, Ani submitted a new supplement (Supplement-8) and we issued a refuse to file letter with CMC comments. This supplement (b) (4) The applicant also made changes to the label.

Previously Neurology was involved with the modern HP Acthar Gel label. We wanted to make you aware of this supplement submission so that you may provide your recommendations or comments.

The reviewers assigned to this NDA (for the meeting request) was Laura Baldassari/ Paul Lee.

EDR Location: \\CDSESUB1\evsprod\NDA008975\0031

Timelines:

Receipt date:	06/29/2021
Tentative Reviews/labeling edits due from reviewers by:	08/10/2021 (let me know if you need additional time)
Internal Meeting:	07/29/2021
PDUFA goal date:	10/29/2021

Clinical reviewer & Team Leader: Geanina Roman-Popoveniuc /Marina Zemskova
CMC reviewer & Team Leader: Pallaiah Thammana/ Zedong Dong

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Dana Smith	☐ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

DANA M SMITH
07/02/2021 03:14:38 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OBP

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Dana Smith
Regulatory Health Project Manager
Division of General Endocrinology (DGE)
Center for Drug Evaluation and Research
Dana.Smith@fda.hhs.gov
240-402-9906

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
07/02/2021	n/a	NDA 008975	Supplement(S-009)	June 29, 2021

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
repository corticotropin injection, USP	standard	n/a	October 1, 2021

NAME OF FIRM: ANI Pharmaceuticals, Inc.'s

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
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- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: Supplement(S-009)

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

We have received a prior approval supplement for NDA 008975/ Purified Cortrophin Gel (Repository Corticotrophin injection) from Ani Pharmaceuticals. In March 2018, we provided a written response to a Type C Meeting, which discuss ANI's proposed strategies for the studies and data required for the re-commercialization of Purified Cortrophin® Gel USP, 80 units/mL. There was a telecon in May 2018 as a follow-up to the meeting. A General Advice Letter was issued May 2018, which provided additional comments to consider for the re-commercialization effort of Purified Cortrophin® Gel USP. There were some concerns about demonstrating safety of the product but no clinical information was submitted. In March 2020, Ani submitted a new supplement (Supplement-8) and we issued a refuse to file letter with CMC comments. The supplement provided detailed CMC information. (b) (4). The applicant also made changes to the label.

Previously OBP was involved with providing comments to the applicant regarding immunogenicity risk assessment . We wanted to make you aware of this supplement submission so that you may provide your recommendations or comments if

necessary.

The reviewers assigned to this NDA (for the meeting request) was Milos Dokmanovic/ Brian Janelsins.

EDR Location: \\CDSESUB1\evsprod\NDA008975\0031

Timelines:

Receipt date:	06/29/2021
Tentative Reviews/labeling edits due from reviewers by:	08/10/2021 (let me know if you need additional time)
Internal Meeting:	07/29/2021
PDUFA goal date:	10/29/2021

Clinical reviewer & Team Leader: Geanina Roman-Popoveniuc /Marina Zemskova
CMC reviewer & Team Leader: Pallaiah Thammana/ Zedong Dong

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Dana Smith	☐ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

DANA M SMITH
07/02/2021 03:01:55 PM

NDA 008975/S-008

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

ANI Pharmaceuticals, Inc.
Attention: Kassidy Good
Director Corticotropin Regulatory Affairs
210 Main Street West
Baudette, MN 56623

Dear Ms. Good:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 008975

SUPPLEMENT NUMBER: 008

PRODUCT NAME: Purified Cortrophin Gel (Repository Corticotrophin Injection USP)

DATE OF SUBMISSION: 03/23/2020

DATE OF RECEIPT: 03/23/2020

This supplemental application proposes the following change for Cortrophin Gel to re-commercialize the 80 U/mL strength to the market [redacted] (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 22, 2020, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be July 23, 2020.

If you have questions, call me at 1-240-402-9906.

Sincerely,

{See appended electronic signature page}

Dana Smith
Regulatory Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

DANA M SMITH
04/02/2020 01:06:25 PM