

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-583

B. Sponsor

Anthony Products Company
5600 Peck Road
Arcadia, CA 91006

C. Proprietary Name

ACTH Gel

D. Established Name

repository corticotropin injection

E. Dosage Form

Injection

F. Route of Administration

Intramuscular for diagnostic use in dogs.
Intramuscular or subcutaneous for a general deficiency of ACTH in dogs and cats.

G. Species/Class

Dogs, Cats

H. Indication

ACTH (adrenocorticotrophic hormone) stimulates the production of cortical hormones by the adrenal cortex. Corticotropin Injection is indicated primarily for use as a diagnostic aid to test for adrenal dysfunction in dogs. The product is also indicated for stimulation of the adrenal cortex, where there is a general deficiency of ACTH in dogs and cats.

II. EFFECTIVENESS

The application is filed as a generic equivalent to Adrenomone (Repository ACTH Injection) for the therapeutic claim. The pioneer product, Adrenomone, was reviewed by the National Academy of Sciences/National Research Council (NAS/NRC) and found to be effective. The Food and Drug Administration (FDA) concurred with the findings that the product was effective. The notice of review was published in the FEDERAL REGISTER Vol. 34, No. 91 dated Tuesday, May 19, 1969.

The firm which holds the approval for the parent product, Adrenomone, has chosen not to market the product for the past 3 years. Therefore, the parent product is not available.

The data from a vasopressin activity test demonstrate the bioequivalency of Anthony's ACTH Gel to the pioneer product reviewed by the NAS/NRC. ACTH Gel conforms to the relevant requirements for "Corticotropin for Injection" USP XXI, p. 250, and is bioequivalent to the pioneer product which meets the same USP standards for vasopressin activity, potency, and assay. The pioneer product was reviewed by the NAS/NRC and judged to be effective for the therapeutic claim; therefore, Anthony's ACTH Gel is also effective.

The application contains reports of 2 well controlled studies from the veterinary literature which establish the efficacy of the diagnostic test claim for ACTH Gel.

- 1) Lorenz, Michael: Diagnosis and Management of Canine Cushing's Syndrome: A Study of 57 Consecutive Cases. Journal of the American Animal Hospital Association. 8:707-716; 1982. The ACTH stimulation test was used as an aid in the diagnosis of spontaneous hyperadrenocorticism in 57 dogs.

Blood samples were collected from each dog for determination of the baseline plasma cortisol concentrations. ACTH gel was administered intramuscularly at 2.2 IU/kg. At 2 hours post-ACTH injection, blood samples were obtained for determination of the plasma cortisol concentrations. Therefore, the dogs served as their own controls.

Plasma cortisol concentrations were determined by either competitive protein-binding radio-assay (CPB) or radioimmunoassay (RIA) techniques.

The results of the plasma cortisol assays for the ACTH stimulation test in the 57 dogs with hyperadrenocorticism are summarized as follows:

CPB (ng / mL)	Pre-ACTH	Post-ACTH
Normal lab value	5-50	80-200
21 dogs - means	87.2	399.0
21 dogs - SD	± 75.4	± 138.9
21 dogs - Range	(10-275)	(220-800)

RIA (ng / mL)	Pre-ACTH	Post-ACTH
Normal lab value	5.0-40.0	80.0-200.0
36 dogs - means	74.40	369.19
36 dogs - SD	± 50. 00	± 116.18
36 dogs - Range	(10-251)	(58-750)

The results of the diagnostic test procedure clearly demonstrate that administration of ACTH gel results in elevation of plasma cortisol concentration in dogs. The difference in the magnitude of the release of cortisol from the adrenal glands in

normal dogs versus dogs with hyperadrenocorticism makes the ACTH stimulation test a useful aid in the diagnosis of adrenal dysfunction.

- 2) Feldman, Edward C. and Peterson, Mark E: Hypoadrenocorticism in Peterson, Mark. E. (ed.) Veterinary Clinics of North America [Small Animal Practice]. Philadelphia: W.B. Saunders, July 1984, pp. 751-766. The ACTH stimulation test was presented as the best means to confirm adrenocortical insufficiency. The test was described using either natural ACTH gel or synthetic ACTH.

Blood samples were collected for measurement of baseline cortisol concentrations in 65 normal dogs and 30 dogs with hypoadrenocorticism.

ACTH gel was administered intramuscularly at 2.2 units/kg. Blood samples were collected at 2 hours post-ACTH injection for determination of plasma cortisol concentration. Therefore, each dog served as its own control.

Subnormal plasma cortisol concentrations following ACTH stimulation established the diagnosis of adrenocortical insufficiency. Dogs with primary or secondary adrenal insufficiency had baseline plasma cortisol concentrations that were either normal or below normal, whereas following ACTH stimulation, plasma cortisol concentrations were below normal and usually similar to the pre-ACTH injection baseline levels.

The data demonstrated that administration of ACTH gel produced an increase in the plasma cortisol concentration above the baseline values in normal dogs and a lack of cortisol elevation in dogs with hypoadrenocorticism.

However, to differentiate primary hypoadrenocorticism from secondary hypoadrenocorticism due to pituitary ACTH failure or chronic iatrogenic corticosteroid administration, the endogenous plasma ACTH concentration should be determined.

Many glucocorticoid preparations, including prednisolone, prednisone and cortisone, cross-react with most cortisol assays to falsely elevate endogenous cortisol determinations. Dexamethasone however, has little or no influence on measurement of endogenous cortisol concentration. Therefore, the authors recommended that to ensure reliable results, prednisolone, prednisone, or cortisone administration should be discontinued 2 to 3 days prior to ACTH stimulation testing.

Two additional reports from the veterinary literature provided protocols for the ACTH diagnostic test procedure and interpretation of the results, to assess adrenal dysfunction in dogs.

- 3) Peterson, Mark E.: Canine Hyperadrenocorticism, in Kirk R.W. (ed.) Current Veterinary Therapy IX. Philadelphia: W.B. Saunders, 1986, pp. 963-972.

The ACTH stimulation test is useful as an aid in the diagnosis of hyperadrenocorticism in dogs. Plasma samples are collected for cortisol determination before and 2 hours after intramuscular administration of ACTH gel.

Results of the ACTH stimulation test are diagnostic for hyperadrenocorticism when the cortisol concentration exceeds the upper limit of normal at 2 hours post ACTH injection.

However, because 85% of dogs with pituitary dependent hyperadrenocorticism (PDH) and over 50% of dogs with hyperadrenocorticism due to adrenocortical tumors

hyperrespond to the ACTH stimulation test, the test cannot reliably distinguish between the two causes of spontaneously occurring hyperadrenocorticism. If hyperadrenocorticism is suspected clinically, the diagnosis should not be excluded based on normal ACTH stimulation test results. Additional tests, such as the high dose dexamethasone suppression test and the determination of endogenous plasma ACTH, may be required to differentiate the causes of spontaneous hyperadrenocorticism.

- 4) Feldman, E.C. and Nelson, R.W.: Canine and Feline Endocrinology and Reproduction. Philadelphia: W.B. Saunders Co., 1987, pp. 161-163 and 207-209.

The ACTH stimulation test is used as an aid in the diagnosis of hyperadrenocorticism (Cushing's syndrome) or hypoadrenocorticism (Addison's disease) in dogs.

Plasma samples are obtained for cortisol determination before and 2 hours following an intramuscular injection of ACTH gel of 2.2 IU/kg (1 IU/lb). The pre- and post-test cortisol concentrations should be compared with the normal values established by the diagnostic laboratory.

In the author's laboratory, normal post-test cortisol concentrations have been determined as between 6 and 17 µg/dl, and cortisol concentrations $\geq$ 20 µg/dl are considered to be consistent with a diagnosis of hyperadrenocorticism. The test does not differentiate pituitary-dependent hyperadrenocorticism (PDH) and functioning adrenocortical tumors. The ACTH stimulation test should be used as a screening test to diagnose hyperadrenocorticism, as the test has been shown to identify hyperadrenocorticism in more than half of the dogs with adrenocortical tumors and in approximately 85% of the dogs with PDH.

An abnormally low concentration of plasma cortisol 2 hours following injection of ACTH gel is diagnostic for hypoadrenocorticism in dogs. However, the ACTH stimulation test does not distinguish hypoadrenocorticism due to primary adrenal disease from secondary adrenal insufficiency due to pituitary failure or chronic iatrogenic corticosteroid administration.

III. TARGET ANIMAL SAFETY

The drug is reviewed by NAS/NRC and deemed safe for the therapeutic claim. FDA concurred with the NAS/NRC findings. No further safety studies have been conducted.

The dosage, frequency, and route of administration recommended for the diagnostic claim are consistent with the NAS/NRC reviewed therapeutic claim for the drug. Therefore, the safety to the target animal is unchanged by the addition of the diagnostic claim for the drug.

IV. HUMAN FOOD SAFETY

Human Food Safety: Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is approved for use only in dogs and cats, which are non-food animals.

Human Safety Relative to Possession, Handling and Administration: Labeling contains adequate caution statement (i.e., veterinary prescription legend).

V. AGENCY CONCLUSIONS

Data submitted satisfy the requirements of Section 512 of the Act and 514.111 of the implementing regulations. The Center for Veterinary Medicine concludes that this product is safe and effective as labeled for the above stated indications. The therapeutic claim, for use in dogs and cats where there is a general deficiency of ACTH, was NAS/NRC reviewed and was found to be effective. FDA concurred with the NAS/NRC findings. The diagnostic claim, for use in dogs to test for adrenal dysfunction, was established in two adequate and well controlled studies published in the veterinary literature (see references 1 and 4 in section 8).

ACTH Gel (Repository Corticotropin Injection) is used as a diagnostic aid to test for adrenal dysfunction in dogs and for therapeutic purposes where there is a general deficiency of ACTH in dogs and cats. The indications for use of ACTH Gel require diagnosis by a licensed veterinarian. Therefore, ACTH Gel is a prescription new animal drug.

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