I. GENERAL INFORMATION

A. File Number

NADA 140-921

B. Sponsor

VET-A-MIX, Inc.
604 West Thomas Avenue
Shenandoah, Iowa 51601-0130

C. Proprietary Name

PrednisTab™

D. Established Name

Prednisolone, USP oral tablet 5.0 mg

E. Dosage Form

5.0 mg compressed tablets

F. Dosage Regimen

The average total daily doses for dogs are as follows:

5 to 15 lb (2 to 7 kg) body weight	2.5 mg
15 to 40 lb (7 to 18 kg) body weight	2.5 to 5 mg
40 to 80 lb (18 to 36 kg) body weight	5 to 10 mg

NOTES: The usual total daily dose of 2.5 mg per 10 pounds of body weight should be given in divided doses, 6 to 10 hours apart

G. Route of Administration

Oral

H. Indication

PrednisTab™ is intended for use in dogs. The indications for PrednisTab™ are the same as those for other anti-inflammatory steroids and comprise the various collagen, dermal, allergic, ocular, otic, and musculoskeletal conditions known to be responsive to the anti-inflammatory corticosteroids. Representative of the conditions in which the use of steroid therapy and the benefits to be derived therefrom have had repeated confirmation in the veterinary literature are: (1) dermal conditions, such as nonspecific eczema, summer dermatitis, and burns; (2) allergic manifestations, such as acute urticaria, allergic dermatitis, drug and serum reactions, bronchial asthma, and pollen sensitivities; (3) ocular conditions, such as iritis, iridocyclitis, secondary glaucoma, uveitis, and chorioretinitis; (4) otic conditions, such as otitis externa; (5) musculoskeletal conditions, such as myositis, rheumatoid arthritis, osteoarthritis, and bursitis; (6) various chronic or recurrent diseases of unknown etiology such asulcerative colitis and nephrosis.

In acute adrenal insufficiency, prednisolone may be effective because of its ability to correct the defect in carbohydrate metabolism and relieve the impaired diuretic response to water, characteristic of primary or secondary adrenal insufficiency. However, because this agent lacks significant mineralocorticoid activity, hydrocortisone sodium succinate, hydrocortisone, or cortisone should be used when salt retention is indicated.

II. EFFECTIVENESS

A. Introduction

The biological and anti-inflammatory activity of methylprednisolone in dogs has been determined by the National Academy of Sciences/National Research Council (NAS/NRC) review to be effective and safe. The April 12, 1969 Federal Register publication reflects the Food and Drug Administration's concurrence with the findings of the NAS/NRC review.

Prednisolone and methylprednisolone are synthetic steroids, which chemically and pharmacologically are very similar, both being classified as corticosteroids. Authoritative standard texts, such as the *United States Pharmacopeia Dispensing Information*(USP DI)(Ref.1); Schleimer, Claman and Oronsky's *Anti-Inflammatory Steroid Action, Basic and Clinical Aspects* (Ref.2); and Goodman and Gilman's *The Pharmacological Basis of Therapeutics* (Ref.4) were consulted. These references indicate that the biochemical mechanism of action of the two drugs is essentially the same.

The basic chemical structure of the glucocorticoids consists of 21 carbon atoms with a total of 4 rings: three 6-carbon rings designated A, B, and C, and a five-carbon ring, D.

Essential features of anti-inflammatory steroids consist of the following: 1) a 2-carbon chain at C-17; 2) methyl groups at C-18 and C-19; 3) a ketone oxygen at C-3; 4) an unsaturated bond between C-4 and C-5; 5) a hydroxyl group at C-11; and 6) a ketone oxygen at C-20. This is depicted by the structure of hydrocortisone (cortisol) in Figure 1.

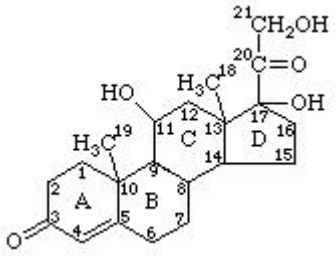


Figure 1. Structure of Hydrocortisone

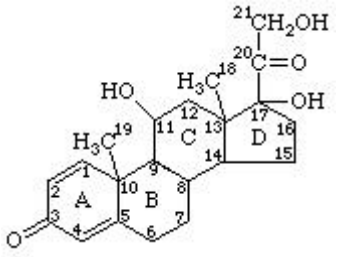


Figure 2. Structure of Prednisolone

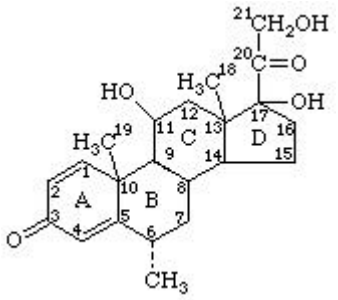


Figure 3. Structure of Methylprednisolone

The introduction of a double bond between C-1 and C-2 as shown in Figure 2 provides the structure for prednisolone, which has a fourfold enhancement of corticosteroid activity as compared to hydrocortisone. The addition of a methyl group at the 6alpha- position of prednisolone forms methylprednisolone as shown in Figure 3. Methylprednisolone is slightly more potent in glucocorticoid activity than prednisolone and has slightly less electrolyte regulating potency than prednisolone.

Available data (Refs.2, 3, 4) suggest a number of similarities in the metabolism of methylprednisolone and prednisolone. Both prednisolone and methylprednisolone undergo continuous enzyme-regulated interconversion by oxidation of the 11beta-hydroxyl group to the 11-keto group and its reduction back to the 11-hydroxy compound, i.e., reversible reactions to prednisolone and methylprednisolone, respectively. The interconversion reaction takes place primarily in the liver and to a lesser extent in the kidney. The reduced, (11beta-hydroxy) forms, prednisolone and methylprednisolone, are the active forms of these corticosteroids in the body.

Reduction of the C-4, 5 double bond in both compounds occurs at both hepatic and extrahepatic sites and yields a metabolite that is inactive. Subsequent reduction in both compounds of the 3-ketone to a 3-hydroxyl to form a tetrahydrocortisol occurs only in the liver. The reduced A-ring metabolites are enzymatically conjugated primarily in the liver and to some extent the kidney with sulfate or with glucuronic acid to form water-soluble sulfate esters or glucuronides, which are excreted in the kidney. Biliary or fecal excretion is not thought to be of quantitative importance.

The major metabolic enzyme involved in the transformation of prednisolone and methylprednisolone include the 11-beta- hydroxy-steroid dehydrogenase and 20-keto-steroid reductase. The metabolic fate of methylprednisolone and

prednisolone may differ slightly and evidence for their interconversion by methylation or demethylation is lacking.

The duration of action of both prednisolone and methylprednisolone are such that their dosage regimes are similar.

The following pharmacokinetic data(Ref.5) (in humans) for methylprednisolone and prednisolone compare the two drugs:

Corticosteroids	**Availability (oral) (%)**	**Urinary Excretion (%)**	**Bound in Plasma (%)**	**Clearance (mL/min kg)**	**Vol. Dist. (liters/kg)**	**Half-Life (hours)**
Methylprednisolone	83±13	4.9±2.3	78±3	6.2±0.9	1.2±0.2	2.3±0.5
Prednisolone	82±13	26±9	90-95	8.7±1.6	1.5±0.2	2.2±0.5

The above data and the following data and discussion support the thesis that absence of the methyl group on prednisolone has little effect on the relative safety and efficacy of prednisolone in the dog. Methylprednisolone tablets in dogs were included in the NAS/NRC review while only prednisolone solution and suspension were reviewed. Accordingly, a bioequivalency study was conducted to demonstrate the comparative bioavailability of Vet-A-Mix's PrednisTab™ (prednisolone) tablets to the approved pioneer product, Upjohn's Medrol® (methylprednisolone) tablets, NADA #11-403, which was the product included in the NAS/NRC review.

B. Pivotal Studies

1. Bioequivalency study

2. The bioequivalency study was conducted by:

   Joseph W. Denhart, DVM, at the College of Veterinary Medicine in the Toxicology section of the Veterinary Diagnostic Laboratory, Iowa State University, Ames, Iowa 50011 for Vet-A-Mix, Inc., Shenandoah, Iowa 51601. The sponsor certifies that the study was performed in compliance with Good Laboratory Practices (21 CFR, Part 58). It was audited by Patricia J. Varilek, an independent Quality Assurance Unit monitor, during critical phases, including dosing, testing and data processing, to certify compliance with GLPs. The dosing dates for Period I and Period II of the crossover study were July 28 and August 18, 1988, respectively. All dogs were additionally tested on July 25 (pre-trial) and August 25 (post-trial) for selected hematologic, serum biochemical and urine parameters.

3. General design of the investigation:

   a. Purpose of the study

      The crossover study was designed to demonstrate bioequivalency of PrednisTab™ (prednisolone 5 mg tablets) and Medrol® (methylprednisolone 1 mg tablets) in dogs.

b. Test animals

Nineteen healthy adult mixed-breed dogs (9 female and 10 male) obtained from Laboratory Animal Resources, Iowa State University were used.

c. Test drug

PrednisTab™ (prednisolone 5 mg tablets)

d. Type of control group

The pioneer product, Medrol® (methylprednisolone 1 mg tablets) was used as an active treatment control. Each animal was tested pre- and post-treatment for control values of test and selected clinical parameters.

e. Diagnosis

Normal animals were used.

f. Dosage form: oral tablets

g. Route of administration: single oral dose

h. Dosages used

A summary of dosing by test groups follows:

Period I	**Medrol®**	**PrednisTab™**
Dose (Dogs <40 lb)	0.27 mg/lb	0.34 mg/lb
Dose (Dogs >40 lb)	0.20 mg/lb	0.25 mg/lb

Period II	**PrednisTab™**	**Medrol®**
Dose (Dogs <40 lb)	0.34 mg/lb	0.27 mg/lb
Dose (Dogs >40 lb)	0.25 mg/lb	0.20 mg/lb

The basis for determining the relative 5:4 milligram dosage of PrednisTab™ versus Medrol® is documented under "Corroborative literary references." Haynes and Murad (Ref.4) show that the relative anti-inflammatory potency of Prednisolone to 6alpha-Methylprednisolone is 4 to 5. The relative sodium retaining potency is 0.8 to 0.5 and the equivalent dosage (mg) is 5 mg for prednisolone and 4 mg for 6alpha-methylprednisolone. Liddle (Ref.3), in comparing the relative effectiveness of 6alpha-methylated and non- methylated steroids on excretion of sodium and potassium in the adrenalectomized dog, show that the relative potency of prednisolone and methylprednisolone to be 3 to 2 respectively. Wilcke and Davis (Ref.6), Ferguson (Ref.8), and Mulnix (Ref.11) all reiterate that the relative anti-inflammatory potency of prednisolone to methylprednisolone is 4 to 5. Medleau (Ref.14) states "Four milligrams of methylprednisolone (Medrol® - Upjohn) is equivalent to 5 mg of prednisone or prednisolone."

i. Test duration

The dogs were acclimated at least 14 days, followed by Period I in which each dog in a group of 9 or 10 dogs was administered a single oral dose of

one of the two drugs. After a washout of 21 days the procedure was repeated in Period II with a reversal of the drug sequence. The dogs were fasted 24 hours before and 24 hours after administration of the drugs at each Period.

j. Pertinent parameters measured

Two biological responses were used to compare the bioactivity of the two drugs, 1) the suppression of circulating eosinophils; and 2) an increase in blood glucose values.

(i) Eosinophil counts

Total circulating eosinophil counts were made at the following times in hours relative to dosing: -12, 0, +2, +4, +6, +8, +12, +18, +24, +36, +48, +72.

(ii) Blood glucose

Blood glucose values were determined at the following times in hours relative to dosing: -12, 0, +2, +4, +6, +8, +12, +18, +24.

(iii) Additional Clinical parameters measured

All dogs were additionally tested 3 days prior to Period I (Pre-trial) and 7 days after Period II (Post-trial) for several hematological and serum biochemical parameters plus urinalysis.

(b) Serum biochemistry (BUN, creatinine, alkaline phosphatase, SGPT and total bilirubin)

(c) Hematology [CBC (RBC, WBC, hemoglobin, packed cell volume) and differential blood count]

(d) Urinalysis (color, transparency, urobilinogen, blood or hemoglobin, bilirubin, ketones and protein)

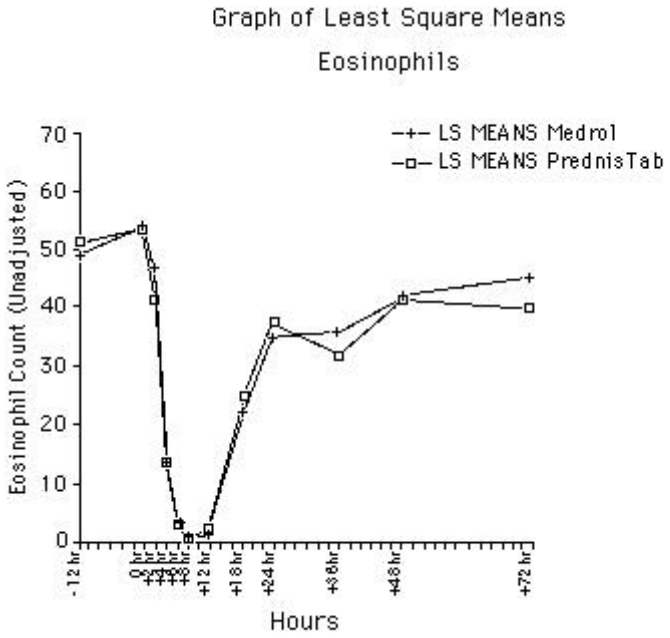
4. Results

a. Eosinophil Counts

The least square mean values for unadjusted eosinophil counts are listed in the following table at each time period for each drug.

	-12 hr	**0 hr**	**+2 hr**	**+4 hr**	**+6 hr**	**+8 hr**	**+12 hr**	**+18 hr**	**+24 hr**	**+36 hr**	**+48 hr**	**+72 hr**
Medrol® Drug A	48.9	54.2	45.2	13.7	3.5	1.0	1.5	22.1	35.0	35.8	41.9	45.3
PrednisTab™ Drug B	51.2	53.2	41.5	13.6	3.1	1.0	2.5	24.5	37.9	31.9	41.1	39.9

These values are unadjusted and need to be multiplied by 17.6 to obtain eosinophils/mm^3



The means, upper and lower 90% confidence intervals, and percentage of the reference drug for AUC, Tmin, and Cmin of eosinophils are listed in the following table.

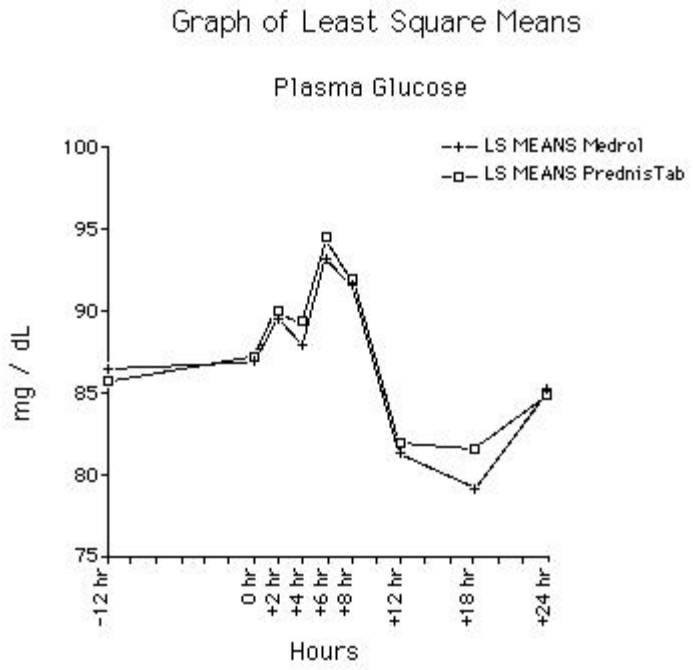
	AUC (mg/dl x hr)	**Tmin (hr)**	**Cmin (mg/dl)**
Medrol® Drug A	2362.99	8.10	0.52
PrednisTab™ Drug B	2275.19	7.81	0.67
Lower 90% C.I.	-394.17	-1.26	-0.41
Upper 90% C.I.	218.57	0.69	0.70
L% of Drug A	-16.68	-15.60	-79.45
U% of Drug A	9.25	8.47	134.77

b. Blood Glucose Concentration

The least square mean values for glucose values are listed in the following table at each time period for each drug.

	-12 hr	**0 hr**	**+2 hr**	**+4 hr**	**+6 hr**	**+8 hr**	**+12 hr**	**+18 hr**	**+24 hr**
Medrol® Drug A	86.2	86.8	89.3	87.9	93.2	91.4	81.1	79.0	85.1
PrednisTab™ Drug B	85.6	86.9	89.8	89.2	94.4	91.8	81.6	81.3	84.5

These are fasted values at each time period.



The means, upper and lower 90% confidence intervals, and percentage of the reference drug for AUC, Tmax, and Cmax for glucose concentrations are listed in the following table.

	AUC (mg/dl x hr)	**Tmin (hr)**	**Cmin (mg/dl)**
Medrol® Drug A	2036.74	5.99	94.82
PrednisTab™ Drug B	2058.57	6.52	96.62
Lower 90% C.I.	-15.37	-1.34	-0.50
Upper 90% C.I.	59.03	2.41	4.10
L% of Drug A	-0.75	-22.42	-0.53
U% of Drug A	2.90	40.23	4.33

c. Additional Clinical Parameters

The mean values for the animals prior to testing and after testing with the normal reference values for the Clinical Pathology Laboratory, Iowa State University, Ames, Iowa are listed below.

Hematology

Parameters Measured	**Normal Values**	**Pre-trial**	**Post-trial**
Hemoglobin gm/dl	12-18	16.9	15.4
Packed Cell Volume	37-55	49.1	45.7
Red Blood Cells	6-9	7.03	6.30
White Blood Cells	6000-17000	10457.9	11021.1
Banded Neutrophils	0-300	0.0	64.9
Segmented Neutrophils	3000-11400	6358.4	6912.0
Lymphocytes	1000-4800	2944.2	2965.1
Monocytes	150-1350	518.6	361.3
Eosinophils	100-750	618.6	706.4
Basophils	0-30	18.1	11.5

Serum Biochemistry

Parameters Measured	**Normal Values**	**Pre-trial**	**Post-trial**
Urea Nitrogen mg/dl	10-30	14.1	13.2
Creatinine mg/dl	0.5-1.5	1.1	1.0
Total Bilirubin	0.1-0.5	0.21	0.18
Alanine Aminotransferase IU/l	0-75	45.3	38.1
Alkaline Phosphatase IU/l	0-150	43.4	41.1

Urinalysis

Parameters Measured	**Normal Values**	**Pre-trial**	**Post-trial**
Specific Gravity	1.015-1.045	1.033	1.028
pH	5-7	6.84	7.18

The following tests were also conducted on urine samples: color, transparency, urobilinogen, blood or hemoglobin, bilirubin, ketones, and protein. All of the clinical pathological parameters examined were within the range of normal accepted values prior to and after the dosing phase of the study.

5. Statistical analysis

   a. Discussion of the statistical results

      (i) Identification of statistical method(s)

      The Draft Bioequivalence Guidelines of CVM, Food and Drug Administration, April 1989, were used for statistical analysis utilizing the confidence interval approach.

(a) Eosinophil Counts

The primary parameters statistically evaluated for eosinophils were area under the curve (AUC), minimum concentration (Cmin) and time to minimum concentration (Tmin).

(b) Blood Glucose Concentrations

The primary parameters statistically evaluated for glucose concentration were area under the curve (AUC), maximum concentration (Cmax) and time to maximum concentration (Tmax).

6. Statistical Results

a. Eosinophil Counts

The lower and upper 90% confidence interval percent of the reference drug for the mean minimum eosinophil count (Cmin) were outside the 20% guidelines. This reflects the number of zero values in the data pool that tended to cause a skewing effect which has invalidated a parametric analysis for Cmin. The lower and upper 90% confidence interval percent of the reference drug for both total area under the curve (AUC) and mean time to minimum eosinophil count (Tmin) are within the 20% guideline limit for acceptance of equal bioactivity. Therefore, Medrol® and PrednisTab™, when dosed at comparative doses, are bioequivalent when considering the anti-inflammatory action of depletion of circulating eosinophils.

b. Blood Glucose Concentrations

The upper and lower 90% confidence interval percent of the reference drug for the mean time to maximum plasma glucose concentration (Tmax) were outside the 20% guideline limits. The difference of approximately one- half hour between the two drugs to attain maximum plasma glucose concentration is too short a time to be biologically or therapeutically significant. The upper and lower 90% confidence interval percent of the reference drug for total area under the curve and maximum glucose concentration (Cmax) are well within the 20% guideline limit for acceptance of equal bioactivity. Therefore, Medrol® and PrednisTab™, when dosed at comparative doses, are bioequivalent when considering the glucocorticoid action of increased plasma glucose concentrations.

7. Conclusions

The biological and anti-inflammatory activity of methylprednisolone in dogs has been determined by the National Academy of Sciences/National Research Council (NAS/NRC) review to be effective and safe. The April 12, 1969 Federal Register publication reflects the Food and Drug Administration's concurrence with the findings of the NAS/NRC review.

The reference drug, methylprednisolone, with a 6-alpha methyl substitution on ring B of the molecule, is an analogue of the test drug, prednisolone.
The bioequivalency of the test drug, Vet-A-Mix's PrednisTab™, compared to the approved reference drug, Medrol®, was studied using two physiological

endpoints, the anti-inflammatory action of the drugs as measured by depletion of circulating eosinophils and the glucocorticoid bioactivity as measured by increased plasma glucose concentration.

Statistical analyses of pharmacokinetic parameters using the confidence interval approach demonstrated bioequivalence of the two drugs. Bioequivalence was shown using the physiological endpoint of eosinophil counts as measured by area under the curve and mean time to minimum eosinophil count. Bioequivalence was shown using the physiological endpoint of increased plasma glucose concentration as measured by area under the curve and maximum glucose concentration.

In addition, the clinical parameters tested indicated that the dogs were essentially normal prior to dosing and that the drugs did not effect any toxicological changes after dosing.

8. Adverse Reactions

   No adverse reactions that could be ascribed to treatments were noted in this study.

III. TARGET ANIMAL SAFETY

The biological and anti-inflammatory activity of methylprednisolone in dogs has been determined by the National Academy of Sciences/National Research Council (NAS/NRC) review to be effective and safe. The April 12, 1969 Federal Register publication reflects the Food and Drug Administration's concurrence with the findings of the NAS/NRC review.

The detailed narrative comparison of methylprednisolone and prednisolone should be referenced from pages 2 to 4. This information, bioequivalency data on pages 7 to 11 and additional clinical parameters measured pre and post- trial on page 10 support the thesis that absence of the 6alpha-methyl group on prednisolone has little effect on the relative safety of prednisolone in the dog. The conclusions of the bioequivalency study may be found on pages 11 and 12.

Corroborative literary references:

1. USP DI. 1989. Adrenocorticoids/corticotropin (systemic- glucocorticoid effects). Pages 71-102 in *Drug Information for the Health Care Professional*, Volume 1A. 9th ed. The United States Pharmacopeial Convention, Rockville, Maryland.
2. Szefler, S. J. 1989. General pharmacology of glucocorticoids. Pages 353-376 in R. P. Schleimer, H. N. Claman and A. L. Oronsky, eds. *Anti-inflammatory Steroid Action: Basic and Clinical Aspects*. Academic Press, Inc., San Diego, California.

The following table provides the relative potencies of prednisolone, methylprednisone, and other corticosteroids.

Table 1. Relative Potencies of Corticosteroids

	Glucocorticoid Potency dose (mg)	**Equivalent Glucocorticoid**	**Mineralocorticoid Potency**	**Plasma t1/2 (min)**	**Biologic t1/2 (hr)**
Short-acting Cortisol	1	25	1	90	8-12
Intermediate-acting Prednisolone	4	5	0	200	12-36
Methylprednisolone	5	4	0	200	12-36
Triamcinolone	5	4	0	200	12-36
Long-acting Betamethasone	25	0.60	0	300	36-54
Dexamethasone	30	0.75	0	300	36-54
Mineralocorticoid Corticosterone	0.35	-	15		
Fludrocortisone	10		125		

Modified from Axelrod, L. 1985. Glucocorticoids. Page 817 in W. N. Kelly, E. D. Harris, S. Ruddy, and C. B. Sledge, eds. *Textbook of Rheumatology*. Saunders, Philadelphia, Pennsylvania.

3. Liddle, G. W. 1958. Studies of structure-function relationship of steroids. II. The 6alpha- methylcorticosteroids. *Metab. Clin. Exp*. 7:405-415. The excerpt from the following table compares the relative excretion of sodium and potassium in the adrenalectomized dog.

Table 1. Relative Effectiveness of 6alpha-Methylated and Non-Methylated Steroids on Excretion of Sodium and Potassium in the Adrenalectomized Dog, using DOC as a Standard

Steriod	**Potency**	**95% Confidence Limit**
Desoxycorticosterone	100	
Hydrocortisone	4	(2-8)
Prednisolone	3	(1-6)
6alpha-methyprednisolone	2	(1-3)

4. Haynes, R. C., Jr. 1990. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. Pages 1431-1462 in A. G. Gilman et al, eds. *The Pharmacological Basis of Therapeutics*. 8th Ed., Pergamon Press, Elmsford, New York. The relative effectiveness of prednisolone and methylprednisolone was reviewed and it was determined that 6alpha- methylprednisolone has slightly greater anti- inflammatory potency and less electrolyte-regulating potency than prednisolone.

   The excerpt from the following table compares the relative potencies and equivalent doses of the three closely related intermediate acting corticosteroids, prednisone, prednisolone, and methylprednisolone and two short acting corticosteroids, hydrocortisone and cortisone.

Table 60-3. RELATIVE POTENCIES AND EQUIVALENT DOSES OF CORTICOSTEROIDS

Compound	**Relative Anti-Inflammatory Potency**	**Relative Sodium-Retaining Potency**	**Duration of Action***	**Approximate Equivalent Dose** (mg)**
Cortisone (11-Dehydrocortisol)	0.8	0.8	S	25
Prednisone (Delta1-Cortisone)	4	0.8	I	5
Cortisol (Hydrocortisone)	1	1	S	20
Prednisolone (Delta1-Cortisol)	4	0.8	I	5
6alpha-Methylprednisolone	5	0.5	I	4

S = short or 8 to 12 hour biological half-life.
* I = intermediate or 12- to 36-hour biological half-life.
** These dose relationships apply only to oral or intravenous administration; relative potencies may differ greatly when injected intramuscularly or into joint spaces.

5. Benet L. Z. and R. L. Williams. 1990. Design and optimization of dosage regimens; pharmacokinetic data. Pages 1650-1735 in A. G. Gilman et al, eds. *The Pharmacological Basis of Therapeutics*. 8th Ed., Pergamon Press, Elmsford, New York.

6. Wilcke, J. R., and L. E. Davis. 1982. Review of glucocorticoid pharmacology. *Vet. Clinics North Am*. 12:3- 17.

   a. Effects on Intermediary Metabolism

      Administration of a glucocorticoid results in an increase in the concentration of glucose in the blood. An increase in gluconeogenesis, a decrease in synthesis of new protein, altered lipid metabolism, and an anti-insulin effect all contribute to this action.

   b. Glucocorticoids as Drugs

      ...prednisone...lacks glucocorticoid activity until it is converted to prednisolone. If hepatic function is in doubt, the active drug prednisolone should be administered in preference to the prodrug prednisone. Synthetic glucocorticoids have been produced to minimize undesirable mineralocorticoid effects and enhance glucocorticoid activity.

Comparison of Corticosteroid Bases

	Anti-inflamatory Potency	**Mineralocorticoid Potency**	**Dose * (mg)**	**Duration ** (hr)**	**Substitutions to Hydrocortisone**
Intermediate-Acting Prednisone	3.5	+	5	12-36	11-ketol;1,2-delta bond
Prednisolone	4.0	+	5	12-36	1,2-delta bond
Methylprednisolone	5.0	0	4	12-36	6-alpha-methyl; 1,2-delta bond

* Daily replacement dose for 20 kg dog
** Length of hypothalamic-pituitary-adrenal suppression

c. Chronic Administration of Glucocorticoids

The wide range of anti-inflammatory and metabolic effects of the glucocorticoids leads to their use in the treatment of a variety of diseases. The general indications for glucocorticoid therapy include ocular disease, hepatic disorders, malignant hematologic disease, solid tumors, intestinal disease, and most prominently immune-mediated and inflammatory-mediated disease.

The most successful approach to minimizing glucocorticoid side effects has been the application of alternate-day therapy.

d. Alternate-day Glucocorticoid Therapy

Any patient being placed on chronic (longer than 14 days) steroid therapy should be considered as a candidate for alternate-day therapy.

Glucocorticoids suitable for this method have a duration of action of 12 to 36 hours. Prednisolone, prednisone, and methylprednisolone are suitable for this method. ...the hypothalamic-pituitary-adrenal axis will be given a steroid-free rest which will allow the axis to maintain some degree of responsiveness to external stimuli.

e. Systemic Effects of Glucocorticoids

Tissue, Organ or Function Effects

Central Nervous System	Euphoria and behavioral changes; maintenance of alpha rhythm; lower seizure threshold
Autonomic Nervous System	Required for normal sensitivity of adrenergic receptors
Gastrointestinal Tract	Decrease absorption of calcium and iron; facilitate absorption of fat; increase secretion of acid, pepsin, and trypsin; alter structure of mucin
Skeletal Muscle	Excess and deficiency cause weakness; excess causes muscle atrophy
Skin	Excess causes atrophy and thinning
Hematopoietic System	Involution of lymphoid tissue; decrease number of peripheral lymphocytes, monocytes and eosinophils; increase number of neutrophils, platelets, and RBCs; decrease clotting time; decrease phagocyte competence
Cardiovascular System	Positive inotropic effect; increase blood pressure due to increased blood volume
Kidneys	Increase reabsorption of water, sodium and chloride; increase potassium and calcium excretion; increase extracellular fluid volume
Bone	Inhibit collagen synthesis by fibroblasts; accelerate bone resorption; antagonize vitamin D
Cells	Stabilize liposomal membranes; inhibit macrophage response to migration inhibiting factor; block sensitization of lymphocytes; block cellular response to inflammatory mediators; inhibit proliferation of fibroblasts
Reproductive Tract	Induce parturition during the latter part of pregnancy in ruminants and horses; effect in dog and cat unknown. Teratogenic during early pregnancy

7. Coppoc, G. L. 1984. Relationship of the dosage form of a corticosteroid to its therapeutic efficacy. *J. Am. Vet. Med. Assoc*. 185:1098-1011. Corticosteroids can be safely and effectively used if the various factors influencing dose and duration of action are considered vis-a'-vis the biological response desired. Consideration of ester, vehicle, physical form, and route are not esoteric exercises, but are critical for rational clinical application of these drugs.

8. Ferguson, D. C. 1985. Rational glucocorticoid therapy in small animals, Part 1. *Mod. Vet. Pract*. 66:101-105.

   a. Though glucocorticoids are widely used in veterinary medicine, there is little objective information available on the efficacy and safety of these drugs in domestic animals. Rational use, therefore, largely depends on clinical experience and extrapolation of data from other species. Clinicians should consider anticipated duration of therapy, individual patient factors, the dose and preparation of glucocorticoid, and alternative modes of therapy that would limit potential side effects of glucocorticoids.

b. Glucocorticoids increase gluconeogenesis, decrease protein anabolism, suppress production of ACTH, TSH, GH and cortisol, inhibit inflammation, cause polyuria, polydipsia, immunosuppression, lymphopenia, eosinopenia, and have positive inotropic and chronotropic cardiac effects. They are only palliative and not curative, and may mask signs of underlying disease. Short-acting glucocorticoids should be used for long-term replacement or alternate-day therapy, while intermediate or long- acting glucocorticoids may be appropriate for initial immunosuppressive or anti-inflammatory therapy.

c. Characteristics of oral glucocorticoids used in small animals are listed in the following table.

Characteristics of Oral Glucocorticoids Used in Small Animals

Drug	**Appropriate for Alternate-Day Therapy**	**Appropriate for Replacement Therapy**	**Approximate Replacement Dose for a 20-kg Dog[1] (mg)**	**Comparative Approximate Mineralocorticoid Activity**
Short-Acting Hydrocortisone	No[2]	Yes	20	1
Cortisone	Yes[3]	Yes	25	1
Prednisolone	Yes	Yes	5	1
Prednisone	Yes	Yes	5	0.2
Methylprednisolone	Yes	Yes	4	0.1
Intermediate-Acting Triamcinolone	No	No	4	0
Long-Acting Flumethasone	No	No	1.5	0
Dexamethasone	No	No	0.75	0
Betamethasone	No	No	0.60	0

[1]Intermediate or long-acting glucocorticoids should not be used for replacement therapy.
[2]Duration of action too short for effective alternate-day therapy.
[3]Not commnly used in small animals for alternate-day therapy because of relatively high expense and short duration of action.

9. MacDonald, J. M. 1987. The use of glucocorticoid therapy in small animal dermatology. *Dermatology Reports*6:8.

a. The practice of dermatology would be extremely compromised without the use of glucocorticoids. Despite their necessity, glucocorticoids are the most overused and abused group of therapeutic agents. With rational use of these drugs, though, the plethora of side effects associated with their administration usually can be prevented. In dermatology, glucocorticoids are used for their anti-inflammatory (pruritic dermatoses such as atopy, flea allergy, scabies) or immunosuppressive (autoimmune dermatoses such as the pemphigus complex, lupus, pemphigoid, vasculitides) effects.

Anticipated duration of therapy is a prime factor in drug selection and regimen of treatment. The specific disease being treated has a bearing on the dosage. Most glucocorticoids are administered systemically; there are fewer indications for topical therapy. Oral administration is preferred because it can be more closely regulated and it is the only safe method of long-term therapy.

b. If the anticipated duration of systemic therapy is less than three to four weeks (short term), the selection of glucocorticoids is not critical; however, if the disease requires long-term therapy (a period of more than three to four weeks), drug selection should be restricted to oral, short-acting drugs. Prednisolone, prednisone, or methylprednisolone is suitable for long-term oral administration.

c. Anti-inflammatory therapy includes induction and maintenance regimes. Induction therapy of an oral glucocorticoid is achieved through the administration of prednisone or prednisolone given SID or divided BID for five to seven days. The anti-inflammatory maintenance dosage may be administered every other morning.

d. Patients requiring maintenance therapy should be placed on an alternate-day regimen. Only short-acting oral glucocorticoids (prednisolone, prednisone, and methylprednisolone) should be used for this purpose. Alternate-day oral treatment with long- or intermediate- acting glucocorticoids such as triamcinolone, dexamethasone, or betamethasone defeats the purpose of alternate-day regimen, which is to provide the hypothalamic-pituitary-adrenal axis a steroid-free rest.

e. Glucocorticoids are an essential part of dermatologic therapy and are relied upon regularly for control of a variety of dermatoses. Side effects are minimized by the alternate-day administration of the smallest effective dose and the exclusion of dermatoses that are not steroid responsive.

10. Ferguson, D. C. 1985. Rational glucocorticoid therapy in small animals, Part II. *Mod. Vet. Pract*. 66:175-179.

    Such short-acting glucocorticoids as hydrocortisone, cortisone, prednisolone and prednisone should be used for replacement therapy or treatment of shock. Glucocorticoids may be used alone or with nonsteroidal drugs for immunosuppression. Nonsteroidal analgesics may be used to supplement the beneficial effects of glucocorticoids in palliative treatment of chronic arthritis or hip dysplasia. Alternate-day glucocorticoid use minimizes side effects and is safer in case of sudden cessation of therapy. Alternate-day therapy should be preceded by a period of daily use and should end with gradually reduced doses. Withdrawal of glucocorticoids should be gradual and prolonged to avoid complications. The ACTH stimulation test is used to assess adrenocortical function. Glucocorticoids should be supplemented in times of stress for animals with adrenocortical insufficiency.

11. Mulnix, J. A. 1977. Corticosteroid therapy in the dog. *Proc. Ann. Am. Anim. Hosp. Assoc*.: 173-179.

a. Anti-inflammatory Potency and Approximate Replacement Dosages for Cortisol (Hydrocortisone) and its Analogues in the Dog.

Compound	**Anti-inflammatory Potency**	**Replacement Dose/Day**	**20 kg Dog**
Short-Acting Hydrocortisone	1.0	1 mg/kg	20 mg
Cortisone	0.8	1.25	25
Prednisone	3.5	0.3	6
Prednisolone	4	0.25	5
Intermediate-Acting Methylprednisolone	5	0.2	4
Triamcinolone	5	0.2	4
Long-Acting Dexamethasone	30	0.03	0.6

b. Rational Use of Corticosteroids in the Dog

(i) Reasons for Using Corticosteroids as Therapeutic Agents

(a) Replacement therapy as in hypoadrenocorticism or following bilateral adrenalectomy

(b) Treat wide variety of nonendocrine disorders - this is the most common reason for their use

(ii) Contraindications to the Indiscriminate Use of Glucocorticoids

(a) Pregnancy

(b) Topical steroids in presence of corneal ulcer

(c) Deep fungal infections

(d) Generalized bone disease (osteoporosis)

(e) Diabetes mellitus

(f) Evidence of chronic infection

(iii) General System Indications for the Glucocorticoids are as follows:

(a) Ocular therapy

Glucocorticoids are a great help in the treatment of noninfectious inflammatory lesions of the eye. The complications that arise due to glucocorticoid use are many. Glaucoma is a steroid-induced condition that seems to be seen only in man and has a genetic link. Posterior subcapsular cataracts have been seen in animals (dogs and rabbits) on high dosages of systemic steroids for prolonged periods.

Steroids are contraindicated if there is any suspicion of a fungal or viral component to an ocular lesion. They will potentiate the problem which could lead to irreversible damage.

Both reversible pupillary dilation and ptosis have been reported with the use of glucocorticoids.

(b) Hepatic disease

Steroids seem to have no beneficial use in treating hepatopathies except in the case of chronic active hepatitis in the dog.

(c) Malignant hematologic diseases

The clinician is mainly concerned with lymphomas, lymphatic leukemia, and multiple myeloma. Glucocorticoids are used for two purposes in treating these disease conditions. First, they seem to directly destroy the neoplastic cells by inhibiting RNA, protein synthesis, and glucose utilization. Secondly, the steroids are useful in treating the secondary complications such as thrombocytopenia, hemolytic anemia and hypercalcemia.

(d) Treatment of solid tumors

The glucocorticoids are used for secondary effects, i.e., hypercalcemia, hemolytic anemia, thrombocytopenia, and cerebral edema associated with metastatic or primary brain tumor.

(e) Shock

There has been much controversy in the use of steroids in shock. The following is a brief summary of the effects of steroids in shock.

(i) Cardiovascular effects

Steroids have not been proven to improve the cardiac output in any case of shock. Corticosteroids do not directly influence vascular responsiveness or function as adrenergic-blocking agents, nor are they direct vasodilators.

(ii) Membrane stability

Steroids are known to stabilize lysosomal membranes which contain acid hydrolases. Corticosteroids can prevent injury to capillary basement membrane and endothelium caused by endotoxin. There is evidence that corticosteroids help to restore the metabolism of underperfused tissue toward normal.

(iii) Metabolic effect

Corticosteroids may reverse some of the metabolic abnormalities associated with oxidative metabolism. In endotoxic shock there is definite benefit due to stabilization of the endothelium and detoxification of the endotoxin.

(f) Intestinal disease

Glucocorticoids have been used in treating ulcerative colitis, regional enteritis and granulomatous colitis. The steroids reduce the inflammatory process along with restoring the integrity of the mucosal lining. The steroids are used for only a brief period of time to stabilize the condition.

(g) Infectious diseases

Steroids should be used only as a last resort measure in those patients with serious infectious diseases. This measure is done more for the comfort of the patient than for treatment of the disease. Corticosteroids alter the host defense mechanism by: (1) suppression of acute and chronic inflammatory responses; (2) alteration of immunologic responsiveness; (3) impairment of the normal intracellular mechanism for disposal of ingested foreign material by phagocytic cells; (4) diminution of interferon synthesis; and (5) interference with healing of the injured tissue.

(h) Allergic disease

The corticosteroids deplete histamine stores and delay resynthesis of histamine by degranulated mast cells. This reduces the hypersensitive and allergic reactions of patients. Steroids also have a direct suppressive action on pruritus. It must be remembered that steroids are only a symptomatic treatment.

(i) Collagen vascular diseases

In this group of diseases are included systemic lupus erythematosus (SLE) and polymyositis. They have responded well to glucocorticoids and should be used in the treatment regimen.

12. Muller, G. H., R. W. Kirk, and D. W. Scott. 1983. *Small Animal Dermatology*. 3rd ed. W. B. Saunders Company, Philadelphia, PA. Pages 166-174. Glucocorticoid Hormone in Dermatologic Therapy

    a. The major indications for glucocorticoid therapy are hypersensitive dermatoses (flea allergy dermatitis, atopy, food hypersensitivity), acute moist dermatitis ("hot spot"), contact dermatitis (irritant or allergic), autoimmune dermatoses (pemphigus, pemphigoid, lupus erythematosus) and acral lick dermatitis.

    b. Of the systemic routes, oral administration is preferred because (1) it can be more closely regulated (a daily dose is more precise than with a repository injection; the drug can be rapidly withdrawn if undesirable side effects occur), and (2) it is the only safe, therapeutic, physiologic way to administer glucocorticoids for more long-term therapy.

    c. Factors that must be considered include the duration of therapy, the personality of the patient, the personality and reliability of the owner, the response of the patient to the drug, the response of the patient's disease to the drug, and other patient-disease considerations.

d. Dermatologically speaking, clinicians usually talk in terms of anti-inflammatory versus immunosuppressive doses, and induction versus maintenance doses of glucocorticoids.

e. Maintenance therapy with oral glucocorticoid is best accomplished with prednisolone, prednisone, or methylprednisolone on an alternate-day basis.

f. Rarely, anti-inflammatory alternate-day glucocorticoid therapy with the preferred prednisolone, prednisone, or methylprednisolone will not be successful. In these cases, the clinician has three therapeutic options (assuming that glucocorticoid therapy is all that can be done): 1) administer prednisolone, prednisone, methylprednisolone on a daily basis, informing the owner of the inevitability of iatrogenic hyperglucocorticoidism; 2) switch to a more potent oral glucocorticoid on an alternate-day basis; or 3) switch to injectable glucocorticoids. Although the more potent oral glucocorticoids are usually not satisfactory for alternate-day therapy (because of potency and duration of effect, they do not spare the hypothalamic-pituitary- adrenal axis).

g. Expected side effects with anti-inflammatory induction therapy include polydipsia, polyuria, and polyphagia. These are usually unavoidable, of little health significance, tolerated by most owners, and eliminated or greatly minimized when alternate-day maintenance therapy is achieved. Far less common, but much more alarming, are behavioral changes (depression, somnolence, viciousness), panting, and diarrhea (which may be bloody). These usually necessitate stopping therapy and often can be minimized or eliminated by switching to a different glucocorticoid.

h. Significant side effects with appropriate anti- inflammatory systemic glucocorticoid regimens are uncommon in dogs, occurring in less than 10 percent of the animals treated. However, with immunosuppressive regimens, the incidence and severity of glucocorticoid side effects escalate alarmingly, and less than 50 percent of the dogs so treated can be satisfactorily managed.

i. Evaluation of results during corticosteroid therapy is very important. The risks of appropriate systemic anti- inflammatory glucocorticoid therapy to an otherwise healthy dog are minimal. The risks of immunosuppressive doses are of greater concern, especially since the medication is usually prescribed for serious or life- threatening diseases.

13. Jenkins, W. L. 1985. Pharmacologic control of inflammation. Pages 127-148 in L. E. Davis, ed. *Handbook of Small Animal Therapeutics*, W. B. Saunders Company, Philadelphia, PA.

Guidelines which should be followed when corticosteroids are administered include the following:

a. Use at correct dosage rate and frequency for a defined and appropriate indication.

b. A single large dose of a glucocorticoid is unlikely to be harmful.

c. Prolonged therapy, at doses above substitution level, may produce harmful effects.

d. Depression of the HHAA may occur and several months are required for recovery to take place.

e. For long-term therapy, early morning alternate-day administration minimizes detrimental effects on the HHAA (use short- or medium-acting corticosteroids).

f. Taper off doses gradually in chronic cases and administer adrenocorticotropic hormone (ACTH) to promote function of depressed adrenal cortex.

g. Recognize disadvantages of long-acting corticosteroids and depo-preparations--especially with regard to HHAA suppression.

h. Long-term therapy should be accompanied by dietary supplementation with high-quality protein, potassium, vitamin A, and vitamin D.

i. The risk/benefit ratio of the concurrent use of corticosteroids and antimicrobial agents should be appraised in each case. Bactericidal antibiotics are preferred.

j. Where acute inflammatory reactions may produce lifelong impairment of an organ's function, early effective doses of corticosteroids are vital.

k. Always recognize that corticosteroids may obscure clinical signs because of the euphoric effects produced, together with improved appetite, reduced fever, pain alleviation, and diminished inflammatory reaction.

Potential Side Effects and Precautions Associated with the Steroids

a. Acute adrenal insufficiency can occur from too rapid withdrawal.

b. Large repetitive doses or prolonged therapy with corticosteroids will result in iatrogenic hypercorticism:

   (i) Fluid and electrolyte disturbances with sodium and water retention, potassium loss, and hypokalemic alkalosis.

   (ii) Hyperglycemia and glycosuria ("steroid diabetes"). Incipient diabetes mellitus may be precipitated.

   (iii) The catabolic effect of the corticosteroids results in a negative nitrogen balance and an increased urea synthesis.

   (iv) Abnormal fat deposition may occur.

   (v) Polydipsia with polyuria and polyphagia.

(vi) Osteoporosis as a result of calcium loss and an increased proneness to fractures.

(vii) Decreased linear growth in growing animals.

(viii) Myopathy, characterized by muscular weakness.

(ix) Acute pancreatitis (rare).

(x) Susceptibility to infection may be increased and encapsulated lesions may break down. Normal wound healing may also be impaired.

(xi) Suppression of normal immune mechanisms.

(xii) Hypercoagulability of blood has been reported.

(xiii) Lymphocytopenia, eosinopenia, and neutrophilia.

(xiv) Temperament changes. An apparent increased feeling of well-being may mask a deterioration in the clinical condition.

(xv) The corticosteroids have been incriminated in the exacerbation of seizures in epileptic patients.

(xvi) Peptic ulceration.

(xvii) Reversible hepatopathy has been described in dogs.

(xviii) Induction and inhibition of drug-metabolizing microsomal enzymes may alter the duration of an animal's response to other drugs.

Effects on laboratory findings may include:

a. Blood

(i) Neutrophilia, monocytosis, lymphopenia, eosinopenia

(ii) Mild polycythemia (?)

(iii) Hyperglycemia

(iv) Blood urea nitrogen (BUN) and creatinine--normal to low

(v) Serum alkaline phosphatase (SAP) increased

(vi) Alanine aminotransferase (AAT) and gamma - glutamyl transpeptidase (GGT) increased

(vii) Lipemia and hypercholesterolemia

(viii) Increased sulfobromophthalein (BSP) retention

(ix) Elevated sodium, depressed potassium, elevated calcium (?)

b. Urine

(i) Dilute urine (S.G. < 2.007)

(ii) Glycosuria

(iii) Calciuria

14. Medleau, L. 1990. Linking chronic steroid-responsive pruritus to allergies. *Vet. Med*. 85:259-271. The major differential diagnoses for dogs with pruritus that resolves with anti-inflammatory doses of steroids are atopy, food-allergic dermatitis, flea-allergic dermatitis, and allergic contact dermatitis. To complicate matters, dogs may have multiple allergies. Intradermal skin testing is used to rule out flea and inhalant allergies. Food allergies are ruled out by feeding the dog a trial hypoallergenic diet. And a diagnosis of allergic contact dermatitis is based on clinical signs, exclusion of other allergic causes, and, if possible, identification of the contact allergen.

15. Chastain, C. G., and C. L. Graham. 1979. Adrenocortical suppression in dogs on daily and alternate-day prednisone administration. *Am. J. Vet. Res*. 40:936-941.

The purpose of this investigation was to evaluate functional and morphologic suppression of the adrenal cortex in dogs given daily physiological doses, daily pharmacological doses, and alternate-day doses of prednisone over a 4-week period.

Three groups of eight normal dogs each were orally given prednisone at doses of 0.22 mg/kg of body weight/day, 0.55 mg/kg/day, or 1.1 mg/kg on alternate mornings. Four dogs served as nontreated controls. Samples were obtained from members of each group to determine baseline serum cortisol and ACTH-stimulated cortisol values and histologic features in the lateral thoracic skin before prednisone administration, and after 1, 2, 3, and 4 weeks of administration. Some animals from each group were necropsied after 1, 2, 3, and 4 weeks of prednisone administration.

Each course of prednisone administration resulted in adrenocortical atrophy and hypofunction, but adrenocortical suppression was less severe and slower in onset in the group given prednisone on alternate days. Extra-adrenal effects observed were atrophy of the skin and focal, fatty change of the liver. These changes were most evident in dogs given daily pharmacologic doses of prednisone (0.55 mg/kg/day). Fewer extra-adrenal effects were observed in dogs given alternate-day therapy. There were no extra-adrenal lesions in the dogs given equivalent glucocorticoid replacement doses (0.22 mg/kg/day).

16. Spencer, K. B., F. N. Thompson, M. D. Lorenz. 1980. Adrenal gland function in dogs given methylprednisolone. *Am. J. Vet. Res*. 41:1503-1506.

Serum cortisol (hydrocortisone) was measured by radioimmunoassay in dogs given methylprednisolone (MP) orally or methylprednisolone acetate (MPA) IM. The MP was given on a daily and on an alternate-day basis to different treatment groups and the MPA was administered weekly. Samples of blood

were obtained twice a week over a 9-week treatment period for serum cortisol determination, and the adrenal gland response to ACTH was assessed on post-treatment days 1, 3, 5, and 7. Administration of MP on an alternate or daily basis caused a slight but significant ($P < 0.05$) depression in mean resting cortisol values over time. The MPA administration caused a severe depression of resting serum cortisol values. In response to ACTH, cortisol values invariably increased sharply in non-treated control dogs and in those dogs given MP on an alternate- day basis. Dogs given MP daily had a depressed response to ACTH. The MPA treatment resulted in adrenal cortices that were unresponsive to ACTH. Dogs given MPA, but not challenge exposed with ACTH, had markedly lowered cortisol values for at least 2 weeks after cessation of treatment. Consequently, a difference between daily- and alternate-day MP administration was detected after ACTH challenge exposure; MPA administration inhibited adrenal cortisol secretion for at least the duration of the experiment.

17. Papich, M. G. and L. E. Davis. 1989. Glucocorticoid Therapy. Pages 54-62 in R. W. Kirk, ed. *Current Veterinary Therapy X*. W. B. Saunders Company, Philadelphia, PA.

    a. Prednisolone suppresses the hypothalamic-pituitary- adrenal (HPA) axis for 24 to 36 hours. Administration of glucocorticoids to dogs for 1 to 2 weeks is unlikely to have a prolonged effect on the adrenal cortex. However, following prolonged administration, adrenal cortical atrophy is possible.

    b. Recovery of adrenal function occurs relatively quickly in dogs after chronic steroid administration.

    c. Although adrenocortical insufficiency following long- term glucocorticoid therapy has been demonstrated in dogs, via ACTH stimulation test results, clinical signs of iatrogenic hypoadrenocorticism have been uncommon.

    d. Potential Adverse Effects of Glucocorticoids

        - Central Nervous System
        - Polyphagia
        - Euphoria
        - Musculoskeletal System
        - Osteoporosis
        - Myopathy
        - Fibroblast inhibition
        - Decreased intestinal calcium absorption
        - Gastrointestinal System
        - GI ulceration
        - Pancreatitis
        - Colonic perforation
        - Fluid Balance
        - Sodium and fluid retention
        - Polyuria and polydipsia
        - Metabolic
        - Hyperlipidemia
        - Lipolysis
        - Protein catabolism

- Fatty infiltration of liver
- Steroid hepatopathy
- Endocrine
- HPA-axis suppression
- Diabetogenic
- Decreased thyroid synthesis
- Increased parathyroid hormone Host Defenses
- Decreased bacterial killing
- Increased risk of septicemia
- Recurrent septic cystitis

18. Nelson, R. W. 1987. Glucocorticoid therapy. Pages 218-228 in E. C. Feldman, ed. Handbook of Canine and Feline Endocrinology and Reproduction. W. B. Saunders Company, Philadelphia, PA.

    a. The oral route for glucocorticoid therapy is preferred in most systemic illnesses. Oral dose forms are usually tablets containing the free steroid alcohol. Oral absorption is usually quite rapid, and plasma half-lives are relatively brief. Unlike many other drugs, however, the duration of glucocorticoid biologic action (as measured by suppression of the hypothalamus and/or pituitary) does not directly parallel the plasma half-life but persists for some time after plasma levels decline. This apparent discrepancy is understood by reiterating that glucocorticoids act by enhancing transcription of both messenger RNA and ribosomal RNA in individual cells, thus creating a wide array of results as well as different durations of action.

    b. Prednisolone and methylprednisolone are considered intermediate (12-36 hours) in duration of action.

    c. Glucocorticoids inhibit inflammation whether the inciting agent is radiant, mechanical, chemical, infectious, or immune-mediated. Such therapy is palliative in that the underlying cause of a disorder may remain but its clinical manifestations are suppressed. This ability to suppress inflammation, regardless of its cause, has made glucocorticoids valuable therapeutic agents. However, these encompassing properties also make glucocorticoid therapy dangerous because these agents are potent at masking the clinical expression of a disease process. The inflammation that allows the clinician to evaluate a chosen course of therapy can be completely suppressed, allowing a disease to continue or worsen but not be identified. As with any therapy, the benefits of glucocorticoid medication must be weighed against the risks of their use.

19. Knecht, C. D., B. Henderson, R. C. Richardson. 1978. Central nervous system depression associated with glucocorticoid ingestion in a dog. *JAVMA*. 173:91-92.

    Signs of a central nervous system disorder were observed following 2 instances of accidental ingestion of glucocorticoid, one time being 250 mg of prednisolone in tablets, in a young female Doberman Pinscher. The signs included transient aggressive and paranoid behavior, amaurosis, disorientation, ataxia with circling backward and depression. Vomiting, weight

loss, and abnormal drinking behavior persisted for several weeks following recovery from the acute illness.

20. Nara, P. L., S. Krakowka, T. E. Powers. 1979. Effects of prednisolone on the development of immune responses to canine distemper virus in beagle pups. *Am. J. Vet. Res*. 40:1742-1747.

    Effects of oral prednisolone (OP) on the development of immune responses of Beagle pups to canine distemper virus (CDV) were studied. Dogs were treated with OP for 21 days, twice a day for the first 7 days, once a day for the next 7 days, and on alternate days for the last 7 days. Dogs given dosages of OP (1 mg/kg and 10 mg/kg) showed a normal in vivo immunogenic response after CDV vaccination and survived a virulent CDV challenge exposure, whereas nontreated, non-vaccinated dogs became ill or died after challenge exposure. The most marked effect of corticosteroid treatment on the immune system was the graded phytoimmunosuppressive effect upon the lymphocyte blast transformation test.

IV. 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 to be labeled for oral use in dogs, which are non-food animals.

V. USER SAFETY

The labeling contains adequate caution/warning statements.

VI. AGENCY CONCLUSIONS

This is a "pipeline DESI" product. This application was filed November 3, 1988 under the Drug Efficacy Study Implementation (DESI) policy for New Animal Drug Applications (NADA), prior to November 16, 1988 enactment of the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) (refer to the fourth policy letter for GADPTRA, November 2, 1989). The NADA, filed under DESI policy, is based on a demonstration of bioequivalence of an approved pre-1962 pioneer product and an "identical, like or related" "me-too" product.

This NADA is for PrednisTab™ (prednisolone) tablets, an oral anti-inflammatory drug for use in dogs. The pre-1962 pioneer product is Medrol® (methylprednisolone) tablets, NADA #11-403, sponsored by the Upjohn Co. The National Academy of Sciences/National Research Council (NAS/NRC) DESI Review determined methylprednisolone tablets to be effective and safe as an oral anti-inflammatory agent for dogs. The April 12, 1969 Federal Register publication reflects the Food and Drug Administration's concurrence with the findings of the NAS/NRC review.

A bioequivalency study comparing the anti-inflammatory activity of the two steroids was completed prior to November 16, 1988 enactment of GADPTRA. Based on the established potency rating of 1 for hydrocortisone, the relative anti-inflammatory potencies of prednisolone and methylprednisolone are 4:5, respectively (A. G. Gilman et al, eds. The Pharmacological Basis of Therapeutics, 8th ed., 1990, p. 1447). The above referenced study conducted by Vet-A-Mix confirmed the relative potencies and

established the bioequivalence of prednisolone/methylprednisolone at a dosage ratio of 5:4, respectively.

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the regulations. It demonstrates that PrednisTab (prednisolone), when used under the labeled conditions of use, is safe and effective.

The approval of this NADA is based on the demonstration of bioequivalency with a pre-1962 NAS/NRC (DESI) reviewed product; therefore, the product does not qualify for marketing exclusivity.

The drug is restricted to use by or on the order of a licensed veterinarian because a knowledge of veterinary medicine is needed for the accurate diagnosis of conditions for which the drug is intended and for determination of appropriate dose, monitoring of treatment, and detection of possible adverse reactions.

VII. ATTACHMENTS

PrednisTab™ 5mg 1000 tablet package label
PrednisTab™ package insert

Copies of these labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.