

Date of Approval: OCT 20 2003

FREEDOM OF INFORMATION SUMMARY

**ORIGINAL ABBREVIATED NEW ANIMAL
DRUG APPLICATION (ANADA)**

ANADA 200-312

DEXIUM

(dexamethasone)

2 mg/mL Injection

Cattle, Horses, Dogs, and Cats

Indications for use: For the treatment of primary bovine ketosis and as an anti-inflammatory agent in cattle, horses, dogs, and cats.

Sponsored by:
Cross Vetpharm Group Ltd.
Tallaght, Dublin 24, Ireland

FREEDOM OF INFORMATION SUMMARY

1. **GENERAL INFORMATION:**

- a. File Number: ANADA 200-312
- b. Sponsor: Cross Vetpharm Group Ltd.
Broomhill Road
Tallaght, Dublin 24, Ireland

Drug Labeler Code: 061623
- c. Established Name: Dexamethasone
- d. Proprietary Name: DEXIUM
- e. Dosage Form: Injectable solution
- f. How Supplied: 100 mL multiple dose vial
- g. How Dispensed: Rx
- h. Amount of Active Ingredient: Each mL contains 2 mg of dexamethasone.
- i. Route of Administration: Intravenously or intramuscularly
- j. Species/Class: Bovine, equine, canine & feline
- k. Recommended Dosage: Bovine - 5 to 20 mg intravenously or intramuscularly.
Equine - 2.5 to 5 mg intravenously or intramuscularly.
Canine - 0.25 to 1 mg intramuscularly or intravenously. The dose may be repeated for three (3) to five (5) days.
Feline - 0.125 to 0.5 mg intravenously or intramuscularly. The dose may be repeated for three (3) to five (5) days.

- l. Pharmacological Category: Anti-inflammatory.
- m. Indications: For treatment of primary bovine ketosis and as an anti-inflammatory agent in the canine, feline, bovine and equine.
- n. Pioneer Product: AZIUM (dexamethasone);
NADA 12-559
Schering-Plough Animal Health

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and drug effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

Ordinarily, the ANADA sponsor shows the generic product is bioequivalent to the pioneer, which has been shown to be safe and effective. If bioequivalence is demonstrated through a clinical endpoint study, then a tissue residue study to establish the withdrawal time for the generic product should also be conducted. For certain dosage forms, the agency will grant a waiver from conducting an *in vivo* bioequivalence study (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 2002).

Based on the formulation characteristics of the generic product, Cross Vetpharm Group Ltd. was granted a waiver from the requirement for *in vivo* bioequivalence study for the generic product DEXIUM (dexamethasone). The generic product is administered as an injectable solution, contains the same active ingredient in the same concentration and dosage form as the pioneer product, and contains no inactive ingredients that may significantly affect the absorption of the active ingredients. The pioneer product, AZIUM (dexamethasone), the subject of Schering-Plough Animal Health, NADA 12-559, was approved on March 29, 1961.

3. HUMAN SAFETY:

• Tolerance

A tolerance is not required because one was not required for the pioneer product.

• Withdrawal Time

A withdrawal period is not required because one was not required for the pioneer product.

• **Regulatory Method for Residues**

A regulatory method is not required because one was not required for the pioneer product.

Human warnings are provided on the product label as follows: **“For Animal Use Only”**
“Keep Out of Reach of Children”

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b)(2) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the Act and demonstrates that DEXIUM, when used under its proposed conditions of use, is safe and effective for its labeled indications.

5. ATTACHMENTS:

Facsimile Generic Labeling and Currently Approved Pioneer Labeling are attached as indicated below:

Pioneer Labeling for NADA 12-559:
AZIUM-100 mL vial size and insert

Generic Labeling for ANADA 200-312
DEXIUM-100 mL vial size and insert

Each cc. contains:
2 mg dexamethasone, 500 mg.
polyethylene glycol 400; 9 mg.
benzyl alcohol, 1.8 mg. methylpar-
aben and 0.2 mg. propylparaben
as preservatives, 0.05 cc alcohol,
water for injection q. s.

100 cc Multiple Dose Vial

Azium[®]
brand of dexamethasone

2
mg
per cc For intravenous
or intramuscular
injection

Sterile
Read accompanying
directions carefully.

SPECIMEN

Caution: Federal law restricts this drug to use
by or on the order of a licensed veterinarian.

Schering



1056412

Schering Corporation, Bloomfield, N.J. 07003

Azium
brand of
dexamethasone
solution

Azium
brand of
dexamethasone
solution



Each cc. contains:
2 mg. dexamethasone; 500 mg.
polyethylene glycol 400; 9 mg.
benzyl alcohol, 1.8 mg.
methylparaben and 0.2 mg.
propylparaben as preservatives,
0.05 cc. alcohol,
water for injection q. s.

Azium
brand of
dexamethasone
solution

100cc. Multiple Dose Vial
Sterile

Azium[®]
brand of
dexamethasone
solution

2
mg
per cc For intravenous
or intramuscular
injection

Caution: Federal law restricts
this drug to use by or on the order of
a licensed veterinarian.



**Veterinary
Schering**

Read accompanying
directions carefully.

4056412

Schering Corporation, Bloomfield, N.J. 07003

F-7008413

**PRODUCT
INFORMATION****AZIUM®****brand of dexamethasone****Aqueous Suspension—2 mg./cc.****for intramuscular injection****Solution—2 mg./cc.****for intravenous or intramuscular injection****Veterinary**

DESCRIPTION AZIUM is a synthetic analogue of prednisolone, having similar but more potent anti-inflammatory therapeutic action and diversified hormonal and metabolic effects. Modification of the basic corticoid structure as achieved in AZIUM offers enhanced anti-inflammatory effect compared to older corticosteroids. The dosage of AZIUM required is markedly lower than that of prednisone and prednisolone:

AZIUM is not specie specific, however, the veterinarian should read the sections on indications, dosage, side effects, contraindications and precautions before this drug is used.

AZIUM Aqueous Suspension is intended for intramuscular administration. Each cc. contains 2 mg. dexamethasone, 10 mg. sodium citrate dihydrate, 0.15 mg. methylcellulose, 9 mg. benzyl alcohol, 1.8 mg. methylparaben and 0.2 mg. propylparaben as preservatives; water for injection q.s.

AZIUM Solution is intended for intravenous or intramuscular administration. Each cc. contains 2 mg. dexamethasone, 500 mg. polyethylene glycol 400, 9 mg. benzyl alcohol, 1.8 mg. methylparaben and 0.2 mg. propylparaben as preservatives, 4.75% alcohol, water for injection q.s.

EXPERIMENTAL STUDIES: Experimental animal studies on dexamethasone have revealed it possesses greater anti-inflammatory activity than many steroids. Veterinary clinical evidence indicates dexamethasone has approximately twenty times the anti-inflammatory activity of prednisolone and seventy to eighty times that of hydrocortisone. Thymus involution studies show dexamethasone possesses twenty-five times the activity of prednisolone. In reference to mineralocorticoid activity, dexamethasone does not cause significant sodium or water retention. Metabolic balance studies show that animals on controlled and limited protein intake will exhibit nitrogen losses on exceedingly high dosages.

INDICATIONS: AZIUM Aqueous Suspension and AZIUM Solution are indicated for the treatment of primary bovine ketosis and as an anti-inflammatory agent in the canine, feline, bovine and equine.

As supportive therapy, AZIUM may be used in the management of various rheumatic, allergic, dermatologic and other diseases known to be responsive to anti-inflammatory corticosteroids. AZIUM Solution may be used intravenously as supportive therapy when an immediate hormonal response is required.

Bovine Ketosis

Both AZIUM Aqueous Suspension and AZIUM Solution are offered for the treatment of primary ketosis. The gluconeogenic effects of AZIUM, when administered intramuscularly, are generally noted within the first 6 to 12 hours. When AZIUM Solution is used intravenously, the effects may be noted sooner. Blood sugar levels rise to normal levels rapidly and generally rise to above normal levels within 12 to 24 hours. Acetone bodies are reduced to normal concentrations usually within 24 hours. The physical attitude of animals treated with AZIUM brightens and appetite improves, usually within 12 hours. Milk production, which is suppressed as a compensatory reaction in this condition, begins to increase. In some instances, it may even surpass previous peaks. The recovery process usually takes from three to seven days.

AZIUM may be used as supportive therapy in mastitis, metritis, traumatic gastritis and pyelonephritis, while appropriate primary therapy is administered. In these cases, the corticosteroid combats accompanying stress and enhances the feeling of general well-being.

AZIUM may also be used as supportive therapy in inflammatory conditions, such as arthritic conditions, snake bite, acute mastitis, shipping fever, pneumonia, laminitis and retained placenta.

Equine

AZIUM is indicated for the treatment of acute musculoskeletal inflammations, such as bursitis, carpalis, osselets, tendonitis, myositis and sprains. If bony changes exist in any of these conditions, joints, or accessory structures, responses to AZIUM cannot be expected. In addition, AZIUM may be used as supportive therapy in fatigue, heat exhaustion, influenza, laminitis and retained placenta provided that the primary cause is determined and corrected.

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AZIUM®

brand of dexamethasone
 Aqueous Suspension—2 mg./cc.
 for intramuscular injection
 Solution—2 mg./cc.
 for intravenous or intramuscular injection
 Veterinary

Canine and Feline

AZIUM as supportive therapy may be used in non-specific dermatosis such as summer eczema and atopy. Primary etiology should be determined and therapy instituted to correct it. The pruritus accompanying these conditions usually subsides within a few hours, followed by regression of inflammatory lesions.

AZIUM may be used as supportive therapy pre- and post-operatively to enhance recovery of poor surgical risks, provided that full antibiotic coverage is instituted.

AZIUM, as supportive therapy, may be used in inflammatory conditions such as acute arthritic conditions. If bony changes exist, response to AZIUM cannot be expected. AZIUM may be used as supportive therapy in canine posterior paresis.

ADMINISTRATION AND DOSAGE Therapy with AZIUM, as with any other potent corticosteroid, should be individualized according to the severity of the condition being treated, anticipated duration of steroid therapy and the animal's threshold or tolerance for steroid excess.

Treatment may be changed over to AZIUM from any other glucocorticoid with proper reduction or adjustment of dosage.

Bovine—AZIUM Solution—5 to 20 mg. intravenously or intramuscularly.

AZIUM Aqueous Suspension—5 to 20 mg. intramuscularly, AZIUM Boluses, AZIUM Powder or AZIUM Oral Solution may be administered or the parenteral dose repeated as needed.

Equine—AZIUM Solution—2.5 to 5 mg. intravenously or intramuscularly.

AZIUM Aqueous Suspension—5 to 20 mg. intramuscularly, AZIUM Boluses, AZIUM Powder, or AZIUM Oral Solution may be administered or the parenteral dose repeated as needed.

Canine—AZIUM Solution—0.25 to 1 mg. intravenously or intramuscularly. The dose may be repeated for three to five days or until a response is noted.

If the condition being treated is of a chronic nature, AZIUM Tablets or AZIUM Oral Solution may be administered at a dose of 0.25 to 0.5 mg. per day as maintenance dosage.

Feline—AZIUM Solution—0.125 to 0.5 mg. intravenously or intramuscularly. The dose may be repeated for three to five days or until a response is noted.

AZIUM Aqueous Suspension—0.125 to 0.5 mg. intramuscularly. The dose may be repeated for three to five days or until a response is noted.

If the condition being treated is of a chronic nature, AZIUM Tablets or AZIUM Oral Solution may be administered at a dose of 0.125 or 0.25 mg. per day as maintenance dosage.

CONTRAINDICATIONS Except for emergency therapy, do not use in animals with chronic nephritis and hypercorticalism (Cushing's syndrome). Existence of congestive heart failure, diabetes and osteoporosis are relative contraindications. Do not use in viral infections during the viremic stage.

PRECAUTIONS Animals receiving AZIUM should be under close observation. Because of the anti-inflammatory action of corticosteroids, signs of infection may be masked and it may be necessary to stop treatment until a further diagnosis is made. Overdosage of some glucocorticoids may result in sodium retention, fluid retention, potassium loss and weight gain.

AZIUM may be administered to animals with acute or chronic bacterial infections providing the infections are controlled with appropriate antibiotic or chemotherapeutic agents.

Doses greater than those recommended in horses may produce a transient drowsiness or lethargy in some horses. The lethargy usually abates in 24 hours.

WARNING Clinical and experimental data have demonstrated that corticosteroids administered orally or parenterally to animals may induce the first stage of parturition when administered during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta, and metritis.

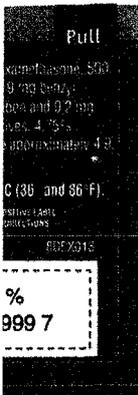
SIDE EFFECTS Side effects, such as weight loss, anorexia, diarrhea, polydipsia, and polyuria have occurred following use of synthetic corticosteroids.

HOW SUPPLIED AZIUM Aqueous Suspension, 2 mg. per cc., 5 cc. multiple dose vial, box of 6.

AZIUM Solution, 2 mg. per cc., 100 cc., multiple dose vial, box of 1.

June, 1970

Schering Corporation
 Bloomfield, N.J. 07003



CAUTION: Federal law restricts this drug to use by or on the order of a veterinarian.

DESCRIPTION: Dexamethasone Solution is a synthetic analogue of prednisolone, having similar but more potent anti-inflammatory therapeutic action and diversified hormonal and metabolic effects. Modification of the basic corticoid structure as achieved in Dexamium™ offers enhanced anti-inflammatory effect compared to older corticosteroids. The dosage of Dexamium™ required is markedly lower than that of prednisone and prednisolone.

Dexamium™ is not species-specific; however, the veterinarian should read the sections on INDICATIONS, DOSAGE, SIDE EFFECTS, CONTRAINDICATIONS, PRECAUTIONS, and WARNINGS before this drug is used.

Dexamium™ is intended for intravenous or intramuscular administration. Each mL contains 2 mg dexamethasone, 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives, 4.75% alcohol, HCl to adjust pH to approximately 4.9, water for injection q.s.

EXPERIMENTAL STUDIES: Experimental animal studies on dexamethasone have revealed it possesses greater anti-inflammatory activity than many steroids. Veterinary clinical evidence indicates dexamethasone has approximately 20 times the anti-inflammatory activity of prednisolone and 70 to 80 times that of hydrocortisone. Thymus involution studies show dexamethasone possesses 25 times the activity of prednisolone. In reference to mineralocorticoid activity, dexamethasone does not cause significant sodium or water retention. Metabolic balance studies show that animals on controlled and limited protein intake will exhibit nitrogen losses on exceedingly high dosages.

INDICATIONS: Dexamium™ is indicated for the treatment of primary bovine ketosis and as an anti-inflammatory agent in the canine, feline, bovine and equine.

As supportive therapy, Dexamium™ may be used in the management of various rheumatic, allergic, dermatologic, and other diseases known to be responsive to anti-inflammatory corticosteroids. Dexamium™ may be used intravenously as supportive therapy when an immediate hormonal response is required.

Bovine Ketosis
 Dexamium™ is offered for the treatment of primary ketosis. The gluconeogenic effects of Dexamium™, when administered intramuscularly, are generally noted within the first 6 to 12 hours. When Dexamium™ is used intravenously, the effects may be noted sooner. Blood sugar levels rise to normal levels rapidly and generally rise above normal levels within 12 to 24 hours. Acetone bodies are reduced to normal concentrations usually within 24 hours. The physical attitude of animals treated with Dexamium™ brightens and appetite improves, usually within 12 hours. Milk production, which is suppressed as a compensatory reaction in this condition, begins to increase. In some instances, it may even surpass previous peaks. The recovery process usually takes from 3 to 7 days.

Supportive Therapy
 Dexamium™ may be used as supportive therapy in mastitis, metritis, traumatic gastritis, and pyelonephritis, while appropriate primary therapy is administered. In these cases, the corticosteroid combats

accompanying stress and enhances the feeling of general well-being.

Dexamium™ may also be used as supportive therapy in inflammatory conditions such as arthritic conditions, snake bite, acute mastitis, shipping fever, pneumonia, laminitis, and retained placenta.

Equine
 Dexamium™ is indicated for the treatment of acute musculoskeletal inflammations, such as bursitis, carpalitis, osselets, tendonitis, myositis, and sprains. If bony changes exist in any of these conditions, joints, or accessory structures, a response to Dexamium™ cannot be expected. In addition, Dexamium™ may be used as supportive therapy in fatigue, heat exhaustion, influenza, laminitis, and retained placenta provided that the primary cause is determined and corrected.

Canine and Feline
 Dexamium™ as supportive therapy may be used in nonspecific dermatosis such as eczema and atopy. Primary etiology should be

ALL TYPE SHOULD BE .125" AWAY FROM EDGE OF DIE LINE

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LEAFLET COPY LAYOUT

MAY 20 2003

BACK OF FRONT PANEL

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 dose vial.

Dexamium™
 DEXAMETHASONE SOLUTION

For intravenous or intramuscular injection
 USUAL DOSE
 Bovine - 5 to 20 mg Canine - 0.25 to 1 mg
 Equine - 2.5 to 5 mg Feline - 0.125 to 0.5 mg

Warning: A withdrawal period has not yet been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal. Read accompanying directions carefully.

FOR ANIMAL USE ONLY
 KEEP OUT OF REACH OF CHILDREN
 Dexamium™ is a trademark of Bimed Inc.
 Manufactured by Bimed/MTC Animal Health Inc.
 Cambridge, Ontario, Canada G2C 2V4

Each mL contains: 2 mg dexamethasone, 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives, 4.75% alcohol, HCl to adjust pH to approximately 4.9, water for injection q.s.

Veterinary 2 mg per mL Sterile

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

ANADA #299-312 Approved by FDA

Net Contents: 100 mL

Manufactured for: Bimed, Inc.
 Riverside, MO 64150

Product No. 128 XXIX BPT XC18

UPC 80%
 0 61133 08999 7

ALL TYPE SHOULD BE .125" AWAY FROM EDGE OF DIE LINE

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4.875"

2ND FOLD

4.625"

18.875"

NON PRINTING AREA
GLUE PANEL

Putt

For intravenous or intramuscular injection.

USUAL DOSE:
 Bovine - 5 to 20 mg Canine - 0.25 to 1 mg
 Equine - 2.5 to 5 mg Feline - 0.125 to 0.5 mg

Warning: A withdrawal period has not yet been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

Read accompanying directions carefully.

FOR ANIMAL USE ONLY
KEEP OUT OF REACH OF CHILDREN
 Dexium™ is a trademark of Bimeda Inc.
 Manufactured by: Bimeda MFG Animal Health Inc.
 Cambridge, Ontario, Canada M3C 2V4

Dexium™
DEXAMETHASONE SOLUTION

Veterinary 2 mg per mL Sterile

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

ANADA #200-312 Approved by FDA

Net Contents: 100 mL

Manufactured for: Bimeda, Inc.
 Riverside, MO 64150

Each mL contains: 2 mg dexamethasone, 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives. 4.75% alcohol. Adjust pH to approximately 4.9, water for injection q.s.

Store between 2° and 30° C (36° and 86° F)

Product No. 10EXXXX N1EX018

UPC 80%
 0 61133 08999 7

5"

ON
MOUNTING
LINE

4.625"

2ND
FOLD

4.875"

1ST
FOLD

18.875"

MAY 20 2003

INSIDE LEAFLET C

5"

ON
MOUNTING
LINE

4.5"

4.875"

determined and therapy instituted to correct it. The pruritus accompanying these conditions usually subsides within a few hours, followed by regression of inflammatory lesions.

Dexium™ may be used as supportive therapy pre- and post-operatively to enhance recovery of poor surgical risks, provided that full antibiotic coverage is instituted.

Dexium™ as supportive therapy, may be used in inflammatory conditions such as acute arthritic conditions. If bony changes exist, a response to Dexium™ cannot be expected. Dexium™ may be used as supportive therapy in canine posterior paresis.

ADMINISTRATION AND DOSAGE: Therapy with Dexium™, as with any other potent corticosteroid, should be individualized according to the severity of the condition being treated, anticipated duration of steroid therapy, and animals threshold or tolerance for steroid excess.

Treatment may be changed over to Dexium™ from any other glucocorticoid with proper reduction or adjustment of dosage.
 Bovine: Dexium™: 5 - 20 mg intravenously or intramuscularly.

Equine: Dexium™: 2.5 - 5 mg intravenously or intramuscularly.
 Canine: Dexium™: 0.25 - 1 mg intravenously or intramuscularly. The dose may be repeated for three (3) to five (5) days.
 Feline: Dexium™: 0.125 - 0.5 mg intravenously or intramuscularly. The dose may be repeated for three (3) to five (5) days.

CONTRAINDICATIONS: Except for emergency therapy, do not use in animals with chronic nephritis and hyper-corticalism (Cushing's syndrome). Existence of congestive heart failure, diabetes, and osteoporosis are relative contraindications. Do not use in viral infections during the viremic stage.

PRECAUTIONS: Animals receiving Dexium™ should be under close observation. Because of the anti-inflammatory action of corticosteroids, signs of infection may be masked and it may be necessary to stop treatment until a further diagnosis is made. Overdosage of some glucocorticoids may result in sodium retention, fluid retention, potassium loss, and weight gain.
 Dexium™ may be administered to animals with acute or chronic

bacterial infections providing the infections are controlled with appropriate antibiotic or chemotherapeutic agents.

Doses greater than those recommended in horses may produce transient drowsiness or lethargy in some horses. The lethargy usually abates in 24 hours.

Use of corticosteroids, depending on the dose, duration, and specified steroid, may result in inhibition of endogenous steroid production following drug withdrawal. In patients presently receiving or recently withdrawn from systemic corticosteroid treatments, therapy with a rapidly acting corticosteroid should be considered in unusually stressful situations.

WARNINGS: Clinical and experimental data have demonstrated that corticosteroids administered orally or parenterally to animals may induce the first stage of parturition when administered during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta, and metritis.

Additionally, corticosteroids administered to dogs, rabbits, and rodents during pregnancy have produced cleft palate. Other congenital anomalies including deformed forelegs, phocomelia, and anasarca have been

reported in offspring of dogs which received corticosteroids during pregnancy.

A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

SIDE EFFECTS: Side effects, such as SAP and SGPT enzyme elevations, weight loss, anorexia, polydipsia, and polyuria, have occurred following the use of synthetic corticosteroids in dogs. Vomiting and diarrhea (occasionally bloody) have been observed in cats and dogs. Cushing's syndrome in dogs has been reported in association with prolonged or repeated steroid therapy.

Corticosteroids reportedly cause laminitis in horses.

HOW SUPPLIED: Dexium™, 2 mg per mL, 100 mL multiple dose vial.

STORAGE: Store between 2° and 30° C (36° and 86° F).