

Approval Date: DEC 19 2007

FREEDOM OF INFORMATION SUMMARY

**ORIGINAL ABBREVIATED NEW ANIMAL DRUG
APPLICATION**

ANADA 200-383

**CLINDAROBE Capsules
(clindamycin hydrochloride)**

**Indicated for the treatment of wounds, abscesses, dental
infections, and osteomyelitis in dogs**

Sponsored by:

Novopharm Ltd.

2008-200-383

FOIS 1

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

- a. File Number: ANADA 200-383
- b. Sponsor: Novopharm Ltd.
30 Novopharm Ct.
Toronto, Ontario, Canada M1B 2K9
- Drug Labeler Code: 043806
- U.S. Agent: Gary W. White, D.V.M.
GCT Consulting Services, Inc.
213 Shiloh Road South
P.O. Box 733
Sallisaw, OK 74955
- c. Established Name: Clindamycin hydrochloride
- d. Proprietary Name: CLINDAROBЕ Capsules
- e. Dosage Form: Capsules
- f. How Supplied: 25 mg bottles of 200 and 600 capsules
75 mg bottles of 200 capsules
150 mg bottles of 100 capsules
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: Each capsule contains 25 mg, 75 mg, or 150 mg clindamycin
- i. Route of Administration: Oral
- j. Species/Class: Dogs
- k. Recommended Dosage: **Infected wounds, abscesses, and dental infections:** 2.5 to 15 mg per pound of body weight every 12 hours for a maximum of 28 days. Treatment of acute infections should not be continued for more than three or four days if no response to therapy is seen.

Osteomyelitis: 5.0 to 15 mg/lb of body weight every 12 hours for a minimum of 28 days. Treatment should not be continued for longer than 28 days if no response to therapy is seen.

- l. Pharmacological Category: Antibacterial
- m. Indications: CLINDAROBЕ Capsules is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:
Dogs: Skin infections (wounds and abscesses) due to coagulase-positive staphylococci (*Staphylococcus aureus* or *Staphylococcus intermedius*). **Deep wounds and abscesses** due to *Bacteroides fragilis*, *Prevotella melaninogenicus*, *Fusobacterium necrophorum*, and *Clostridium perfringens*. **Dental infections** due to *Staphylococcus aureus*, *Bacteroides fragilis*, *Prevotella melaninogenicus*, *Fusobacterium necrophorum* and *Clostridium perfringens*. **Osteomyelitis** due to *Staphylococcus aureus*, *Bacteroides fragilis*, *Prevotella melaninogenicus*, *Fusobacterium necrophorum*, and *Clostridium perfringens*.
- n. Pioneer Product: ANTIROBE; clindamycin hydrochloride; NADA 120-161; Pharmacia & Upjohn Co., a Division of Pfizer, Inc.

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 effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

A. Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and pioneer formulations of 150-mg clindamycin hydrochloride capsules.

Protocol Title: Two-Way Crossover Bioequivalence Study of Novopharm and Upjohn (ANTIROBE) 150 Mg Clindamycin Hydrochloride Capsules in Beagle Dogs

Testing Facility: LAB Pre-Clinical Research International Inc.
560 Cartier Blvd West
Laval, Quebec, Canada H7V 1J1

Study Number: 980221

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence of Novopharm clindamycin hydrochloride 150-mg capsules and Upjohn ANTIROBE 150-mg capsules following oral administration of a single dose in a two period crossover study in dogs.

Summary: In the single-dose, two period, two sequence bioavailability study, 18 healthy female beagle dogs were randomized to two sequences in equal number. The dogs were administered an oral dose of 150-mg capsules clindamycin hydrochloride of either the Novopharm CLINDAROBÉ formulation followed by the Upjohn ANTIROBE formulation or vice-versa. A 7-day washout period was observed. For each period of the study, pre-dose blood samples were taken and sampling continued with post-dose samples taken at 10, 20, 30, 40, 50, 60, 80, 100 minutes, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours post-dosing.

Results: The area under the curve (AUC) was estimated using the trapezoidal rule including data from time 0 to the last sampling time associated with quantifiable drug concentrations. The maximum concentration measured for all time periods (C_{MAX}) was estimated. The natural logarithm of both AUC and C_{MAX} was computed and used as the variable for analysis.

The criteria for determining bioequivalence, as described in CVM's Bioequivalence Guidance is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the log scale of AUC and C_{MAX} and then take the anti-log of the confidence limits multiplied by 100. The resulting bounds should be between 80.00% and 125.00%. As seen in the table below, both AUC and C_{MAX} fall within those bounds.

Table: Comparative Bioequivalence Criteria for the Test and Reference Products

Variable	CLINDAROBÉ Mean	ANTIROBE Mean	Lower Bound	Upper Bound
AUC ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	22842.9.8*	20669.3*	99.6%	122.7%
C_{MAX} ($\mu\text{g}/\text{mL}$)	6120.6*	5935.5*	94.4%	112.7%
T_{MAX} (hr)	0.94 [†]	0.87 [†]	NA	NA

* Geometric Mean
† Arithmetic Mean

The variable time to maximum concentration (T_{MAX}) is permitted to be interpreted by clinical judgment. In this case, there is no reason to expect the difference in T_{MAX} will affect the efficacy of the drug since both AUC and C_{MAX} are bioequivalent and the product is administered as a single dose.

Because both AUC and C_{MAX} are bioequivalent and T_{MAX} is acceptable, the study objective to determine the bioequivalence of the generic and pioneer products was achieved.

B. Dissolution Study

In vitro dissolution data were submitted in support of the request for waiver of *in vivo* bioequivalence study requirements for the 25 and 75 mg strength capsules. The *in vitro* dissolution data were generated in accordance with USP method (900 mL freshly degassed phosphate buffer, pH 6.8, using Apparatus 1 at 100 rpm). The sponsor also provided information confirming that the inactive ingredients for the Novopharm product do not interfere with the refractive index detection used for quantitating the amount of clindamycin dissolved in the dissolution buffer (tested against the standard solution).

The comparative *in vitro* dissolution data demonstrated that 85% clindamycin was rapidly dissolved within 15 minutes for all strengths of the test and reference products, therefore the f_2 calculation was deemed unnecessary. Thus, comparable *in vitro* dissolution profiles generated with the test and reference products for the 25 mg, 75 mg, and 150 mg strength capsules were acceptable. Additionally, compositional dose proportionality data for the all three strengths of the generic clindamycin capsules were determined to be acceptable. Based upon these conclusions and the acceptable *in vivo* bioequivalence study comparing the 150 mg strength of the test and reference products, a waiver of *in vivo* bioequivalence study requirements for Novopharm Ltd.'s 25 mg and 75 mg strength capsules was granted.

3. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

Human Warnings are provided on the product label as follows:

“Keep out of the reach of children.”

“Not for human use.”

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that CLINDAROBÉ Capsules, 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:

Generic Labeling for ANADA 200-383:

CLINDAROBЕ Capsules –

Package Insert

25 mg bottles of 200 and 600 capsules

75 mg bottles of 200 capsules

150 mg bottles of 100 capsules

Pioneer Labeling for NADA 120-161:

ANTIROBE –

Package Insert

25 mg bottles of 600 capsules

75 mg bottles of 200 capsules

150 mg bottles of 100 capsules



A Division of LLOYD, Inc.

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For Veterinary
Use Only

ClindaRobe™
Capsules

(clindamycin hydrochloride)

70246IN-4600 Rev. 00

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

DESCRIPTION

ClindaRobe™ Capsules contain clindamycin hydrochloride which is the hydrated salt of clindamycin. Clindamycin is a semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of a naturally produced antibiotic produced by *Streptomyces lincolnensis* var. *lincolnensis*.

ClindaRobe™ Capsules
(For Use in Dogs Only):

25mg Capsule - Each opaque white body and opaque yellow cap, size#3 hard gelatin capsules; imprinted in black ink nv and 25 on opposing cap and body portions of the capsule contains clindamycin hydrochloride equivalent to 25 mg of clindamycin.

75mg Capsule - Each opaque white body and opaque dark green cap, size#3 hard gelatin capsules; imprinted in black ink nv and 75 on opposing cap and body portions of the capsule contains clindamycin hydrochloride equivalent to 75 mg of clindamycin.

150mg Capsule - Each opaque maroon cap and opaque amethyst body, size#1 hard gelatin capsules; printed in white ink N and 150 on opposing cap and body portions of the capsule contains clindamycin hydrochloride equivalent to 150 mg of clindamycin.

ACTIONS

Site and Mode of Action: Clindamycin is an inhibitor of protein synthesis in the bacterial cell. The site of binding appears to be in the 50S sub-unit of the ribosome. Binding occurs to the soluble RNA fraction of certain ribosomes, thereby inhibiting the binding of amino acids to those ribosomes. Clindamycin differs from cell wall inhibitors in that it causes irreversible modification of the protein-synthesizing subcellular elements at the ribosomal level.

Microbiology: Clindamycin is a lincosaminide antimicrobial agent with activity against a wide variety of aerobic and anaerobic bacterial pathogens. Clindamycin is a bacteriostatic compound that inhibits bacterial protein synthesis by binding to the 50S ribosomal sub-unit. The minimum inhibitory concentrations (MICs) of Gram-positive and obligate anaerobic pathogens isolated from dogs in the United States are presented in Table 1. Bacteria were isolated in 1998-1999. All MICs were performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS).

Table 1. Clindamycin MIC Values (µg/mL) from Diagnostic Laboratory Survey Data Evaluating Canine Pathogens in the U.S. During 1998-99¹

Organism	Number of Isolates	MIC ₅₀	MIC ₈₅	MIC ₉₀	Range
Soft Tissue/Wound²					
Staphylococcus aureus	17	0.5	0.5	≥4.0	0.25-≥4.0
Staphylococcus intermedius	28	0.25	0.5	≥4.0	0.125-≥4.0
Staphylococcus spp.	18	0.5	0.5	≥4.0	0.25-≥4.0
Beta-hemolytic streptococci	46	0.5	0.5	≥4.0	0.25-≥4.0
Streptococcus spp.	11	0.5	≥4.0	≥4.0	0.25-≥4.0
Osteomyelitis/Bone³					
Staphylococcus aureus	20	0.5	0.5	0.5	0.5 ⁴
Staphylococcus intermedius	15	0.5	≥4.0	≥4.0	0.25-≥4.0
Staphylococcus spp.	18	0.5	≥4.0	≥4.0	0.25-≥4.0
Beta-hemolytic streptococci	21	0.5	2.0	2.0	0.25-≥4.0
Streptococcus spp.	21	≥4.0	≥4.0	≥4.0	0.25-≥4.0

Organism	Number of Isolates	MI ₅₀	MI ₇₅	MI ₉₀	Range
Dermal/Skins ⁵					
Staphylococcus aureus	25	0.5	≥4.0	≥4.0	0.25-≥4.0
Staphylococcus intermedius	48	0.5	≥4.0	≥4.0	0.125-≥4.0
Staphylococcus spp.	32	0.5	≥4.0	≥4.0	0.25-≥4.0
Beta-hemolytic streptococci	17	0.5	0.5	0.5	0.25-0.5

¹ The correlation between the *in vitro* susceptibility data and clinical response has not been determined.

² Soft Tissue/Wound: includes samples labeled wound, abscess, aspirate, exudates, draining tract, lesion, and mass

³ Osteomyelitis/Bone: includes samples labeled bone, fracture, joint, tendon

⁴ No range, all isolates yielded the same value

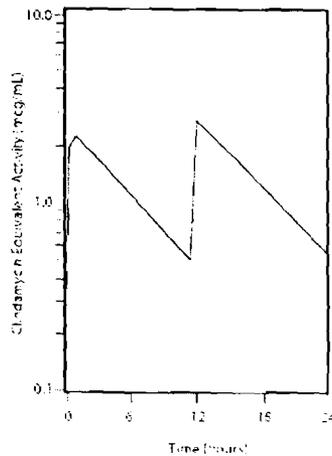
⁵ Dermal/Skin: includes samples labeled skin, skin swab, biopsy, incision, lip

PHARMACOLOGY

Absorption: Clindamycin hydrochloride is rapidly absorbed from the canine gastrointestinal tract.

Dog Serum Levels: Serum levels at or above 0.5 µg/mL can be maintained by oral dosing at a rate of 2.5 mg/lb of clindamycin hydrochloride every 12 hours. This same study revealed that average peak serum concentrations of clindamycin occur 1 hour and 15 minutes after oral dosing. The elimination half-life for clindamycin in dog serum was approximately 5 hours. There was no bioactivity accumulation after a regimen of multiple oral doses in healthy dogs.

Clindamycin Serum Concentrations
2.5 mg/lb (5.5 mg/kg)
After B.I.D. Oral Dose of clindamycin hydrochloride capsules to Dogs



METABOLISM AND EXCRETION

Extensive studies of the metabolism and excretion of clindamycin hydrochloride

METABOLISM AND EXCRETION

Extensive studies of the metabolism and excretion of clindamycin hydrochloride administered orally in animals and humans have shown that unchanged drug and bioactive and bioinactive metabolites are excreted in urine and feces. Almost all of the bioactivity detected in serum after clindamycin hydrochloride product administration is due to the parent molecule (clindamycin). Urine bioactivity, however, reflects a mixture of clindamycin and active metabolites, especially N-demethyl clindamycin and clindamycin sulfoxide.

ANIMAL SAFETY SUMMARY

Rat and Dog Data: One year oral toxicity studies in rats and dogs at doses of 30, 100 and 300 mg/kg/day (13.6, 45.5 and 136.4 mg/lb/day) have shown clindamycin hydrochloride to be well tolerated. Differences did not occur in the parameters evaluated to assess toxicity when comparing groups of treated animals with contemporary controls. Rats administered clindamycin hydrochloride at 600 mg/kg/day (272.7 mg/lb/day) for six months tolerated the drug well; however, dogs orally dosed at 600 mg/kg/day (272.7 mg/lb/day) vomited, had anorexia, and subsequently lost weight. At necropsy these dogs had erosive gastritis and focal areas of necrosis of the mucosa of the gallbladder.

Safety in gestating bitches or breeding males has not been established.

INDICATIONS

ClindaRobe™ Capsules

(for use in dogs only) is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

Dogs: Skin infections (wounds and abscesses) due to coagulase positive staphylococci (*Staphylococcus aureus* or *Staphylococcus intermedius*). **Deep wounds and abscesses** due to *Bacteroides fragilis*, *Prevotella melaninogenica*, *Fusobacterium necrophorum* and *Clostridium perfringens*.

Dental infections due to *Staphylococcus aureus*, *Bacteroides fragilis*, *Prevotella melaninogenica*, *Fusobacterium necrophorum* and *Clostridium perfringens*.

Osteomyelitis due to *Staphylococcus aureus*, *Bacteroides fragilis*, *Prevotella melaninogenica*, *Fusobacterium necrophorum* and *Clostridium perfringens*.

CONTRAINDICATIONS

ClindaRobe™ Capsules are contraindicated in animals with a history of hypersensitivity to preparations containing clindamycin or lincocmycin.

Because of potential adverse gastrointestinal effects, do not administer to rabbits, hamsters, guinea pigs, horses, chinchillas or ruminating animals.

WARNINGS

Keep out of reach of children. Not for human use.

PRECAUTIONS

During prolonged therapy of one month or greater, periodic liver and kidney function tests and blood counts should be performed.

The use of clindamycin hydrochloride occasionally results in overgrowth of non-susceptible organisms such as clostridia and yeasts. Therefore, the administration of **ClindaRobe™ Capsules** should be avoided in those species sensitive to the gastrointestinal effects of clindamycin (see **CONTRAINDICATIONS**). Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Patients with very severe renal disease and/or very severe hepatic disease

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy.

Clindamycin hydrochloride has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, clindamycin hydrochloride should be used with caution in animals receiving such agents.

Safety in gestating bitches or breeding male dogs has not been established.

ADVERSE REACTIONS

Side effects occasionally observed in either clinical trials or during clinical use were vomiting and diarrhea.

To report adverse reactions or a suspected adverse reaction call 1-800-831-0004.

DOSAGE AND ADMINISTRATION

Dogs:

Infected Wounds, Abscesses and Dental Infections

Oral: 2.5-15.0 mg/lb body weight every 12 hours.

Duration: Treatment with ClindaRobe™

Capsules may be continued up to a maximum of 28 days if clinical judgment indicates. Treatment of acute infections should not be continued for more than three or four days if no response to therapy is seen.

Dosage Schedule:

ClindaRobe™ Capsules 25 mg, administer 1-6 capsules every 12 hours for each 10 pounds of body weight.

ClindaRobe™ Capsules 75 mg, administer 1-6 capsules every 12 hours for each 30 pounds of body weight.

ClindaRobe™ Capsules 150 mg, administer 1-6 capsules every 12 hours for each 60 pounds of body weight.

Osteomyelitis

Oral: 5.0-15.0 mg/lb body weight every 12 hours.

Duration: Treatment with ClindaRobe™ **Capsules** is recommended for a minimum of 28 days. Treatment should not be continued for longer than 28 days if no response to therapy is seen.

Dosage Schedule:

ClindaRobe™ Capsules 25 mg, administer 2-6 capsules every 12 hours for each 10 pounds of body weight.

ClindaRobe™ Capsules 75 mg, administer 2-6 capsules every 12 hours for each 30 pounds of body weight.

ClindaRobe™ Capsules 150 mg, administer 2-6 capsules every 12 hours for each 60 pounds of body weight.

HOW SUPPLIED

ClindaRobe™ Capsules are supplied as:
25 mg - bottles of 200...NDC 43806-074-53
bottles of 600...NDC 43806-074-74

75 mg - bottles of 200...NDC 43806-075-53

150 mg - bottles of 100...NDC 43806-076-40

ANADA # 200-383, approved by FDA

To report a suspected adverse reaction or to request a material safety data sheet (MSDS), call 1-800-831-0004.

Store at controlled room temperature 20° to 25° C (66° to 77° F) [See USP].

Made in Canada for
Vet-A-Mix, A Division of Lloyd Inc,
Shenandoah, Iowa

75 mg - bottles of 200....NDC 43806-076-33

150 mg - bottles of 100....NDC 43806-076-40

ANADA # 200-383, approved by FDA

To report a suspected adverse reaction or
to request a material safety data sheet
(MSDS), call 1-800-831-0004.

Store at controlled room temperature
20° to 25° C (66° to 77° F) [See USP].

Made in Canada for
Vet-A-Mix, A Division of Lloyd Inc,
Shenandoah, Iowa
51601

by
Novopharm Limited
30 Novopharm Court
Toronto, Canada
M1B 2K9

0305

Revised August 2007
70246IN-4600 Rev. 00

Approved for use in dogs.

Recommended Dosage:

For therapy of wounds, abscesses and dental infections, 10 capsules for each 10 pounds body weight every 12 hours.

For therapy of osteomyelitis, 2-6 capsules for each 10 pounds body weight every 12 hours.

See package insert for complete product information.

Warning: Keep out of reach of children. Not for human use. Keep container tightly closed. Store at controlled room temperature 20° to 25°C (68° to 77°F).

NDC 43906-074-53
ClindaRobe™

Capsules

(Clindamycin Hydrochloride)

Equiv. to 25 mg clindamycin

For Use in Dogs Only

200 Capsules

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

ANADA # 200-383. Approved by FDA



Each Capsule Contains:

Clindamycin Hydrochloride equivalent to Clindamycin..... 25 mg

Made in Canada for

by

Division of Lloyd, Inc.

Shawandee, Iowa 51801

By

Pharmogen, Limited

Toronto, Canada

MIB 2x9

70266-483 Rev. 00
8 9505 32701 1

Approved for use in dogs.

Recommended Dosage:

For therapy of wounds, abscesses and dental infections, 1-6 capsules for each 10 pounds body weight every 12 hours.

For therapy of osteomyelitis, 2-8 capsules for each 10 pounds body weight every 12 hours.

See package insert for complete product information.

Warning: Keep out of reach of children. Not for human use. Keep container tightly closed. Store at controlled room temperature 20° to 25°C (68° to 77°F).

NDC 43806-074-74

**ClindaRobe™
Capsules**

(Clindamycin Hydrochloride)

█
Equiv. to 25 mg clindamycin

For Use in Dogs Only

600 Capsules

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

ANADA # 200-383, Approved by FDA



Each Capsule Contains:

Clindamycin Hydrochloride
equivalent to Clindamycin.....25 mg

Made in Canada for
Vet-A-Mix
a Division of Lloyd, Inc.
Shenandoah, Iowa 51801
By
Novopharm Limited
Toronto, Canada
M1B 2K9

List 2702

70246LA-4674 Rev. 00



Approved for use in dogs.

Recommended Dosage:

For therapy of wounds, abscesses and dental infections, 1-6 capsules for each 30 pounds body weight every 12 hours.

For therapy of osteomyelitis, 2-6 capsules for each 30 pounds body weight every 12 hours.

See package insert for complete product information.

Warning: Keep out of reach of children. Not for human use. Keep container tightly closed. Store at controlled room temperature 20° to 25°C (68° to 77°F).

NDC 43806-075-53

ClindaRobe™
Capsules
(Clindamycin Hydrochloride)

Equiv. to 75 mg clindamycin

For Use in Dogs Only
200 Capsules

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

ANADA # 200-383, Approved by FDA



Each Capsule Contains:

Clindamycin Hydrochloride
equivalent to Clindamycin.....75 mg

Made in Canada for
Vet-Mix
a Division of Lloyd, Inc.
Shenandoah, Iowa 51601
L81 2711
By
Novopharm Limited
Toronto, Canada
M1B 2G6
70248LA-4953 Rev. 00



Approved for use in dogs.

Recommended Dosage:
For therapy of wounds, abscesses and
dermal infections, 1-6 capsules for each
60 pound body weight every 12 hours.

For therapy of osteomyelitis,
2-6 capsules for each 60 pounds
body weight every 12 hours.

See package insert for complete
product information.

Warning: Keep out of reach of children.
Not for human use. Keep container
tightly closed. Store at controlled room
temperature 20° to 25°C (68° to 77°F).

NDC 43906-076-40

ClindaRobel™ Capsules

(Clindamycin Hydrochloride)

150 mg

Equivalent to 150 mg clindamycin
For Use in Dogs Only

100 Capsules

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

ANANDA # 200-383, Approved by FDA



Each Capsule Contains:

Clindamycin Hydrochloride
equivalent to Clindamycin..... 150 mg

Made in Canada for
Vet-Mix of Lund, Inc.
Sawmills, Iowa 51801
Lot 2721

By: **Pharmchem Limited**
Toronto, Canada
L7R 2Z6

7 89561 32721 9

Antirobe®
brand of clindamycin
hydrochloride capsules, USP
Antirobe Aquadrops®
brand of clindamycin hydrochloride liquid

Pharmacia
&Upjohn

Antirobe
brand of clindamycin hydrochloride capsules, USP
Antirobe Aquadrops
brand of clindamycin hydrochloride liquid

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

DESCRIPTION

ANTIROBE Capsules and ANTIROBE AQUADROPS Liquid contain clindamycin hydrochloride which is the hydrated salt of clindamycin. Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chlorosubstitution of the 7(R)-hydroxyl group of a naturally produced antibiotic produced by *Streptomyces lincolnensis* var. *lincolnensis*.

ANTIROBE Capsules (For Use in Dogs Only):
25 mg Capsule, each yellow and white capsule contains clindamycin hydrochloride equivalent to 25 mg of clindamycin.

75 mg Capsule, each green capsule contains clindamycin hydrochloride equivalent to 75 mg of clindamycin.

150 mg Capsule, each light blue and green capsule contains clindamycin hydrochloride equivalent to 150 mg of clindamycin.

300 mg Capsule, each light blue capsule contains clindamycin hydrochloride equivalent to 300 mg of clindamycin.

ANTIROBE AQUADROPS Liquid (For Use in Dogs and Cats) is a palatable formulation intended for oral administration. Each mL of ANTIROBE AQUADROPS Liquid contains clindamycin hydrochloride equivalent to 25 mg clindamycin; and ethyl alcohol, 8.64%.

ACTIONS

Site and Mode of Action: Clindamycin is an inhibitor of protein synthesis in the bacterial cell. The site of binding appears to be in the 50S sub-unit of the ribosome. Binding occurs to the soluble RNA fraction of certain ribosomes, thereby inhibiting the binding of amino acids to those ribosomes. Clindamycin differs from cell wall inhibitors in that it causes irreversible modification of the protein-synthesizing subcellular elements at the ribosomal level.

MICROBIOLOGY: Clindamycin is a lincosamide antimicrobial agent with activity against a wide variety of aerobic and anaerobic bacterial pathogens. Clindamycin is a bacteriostatic compound that inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit. The minimum inhibitory concentrations (MICs) of Gram-positive and obligate anaerobic pathogens isolated from dogs and cats in the United States are presented in Table 1 and Table 2. Bacteria were isolated in 1998-1999. All MICs were performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS).

Antirobe
brand of clindamycin hydrochloride capsules, USP
Antirobe Aquadrops
brand of clindamycin hydrochloride liquid

Table 1. Clindamycin MIC Values ($\mu\text{g/mL}$) from Diagnostic Laboratory Survey Data Evaluating Canine Pathogens in the U.S. during 1998-99¹

Organism	Number of Isolates	MIC ₅₀	MIC ₈₅	MIC ₉₀	Range
Soft Tissue/Wound²					
<i>Staphylococcus aureus</i>	17	0.5	0.5	≥ 4.0	0.25- ≥ 4.0
<i>Staphylococcus intermedius</i>	28	0.25	0.5	≥ 4.0	0.125- ≥ 4.0
<i>Staphylococcus</i> spp.	18	0.5	0.5	≥ 4.0	0.25- ≥ 4.0
Beta-hemolytic streptococci	46	0.5	0.5	≥ 4.0	0.25- ≥ 4.0
<i>Streptococcus</i> spp.	11	0.5	≥ 4.0	≥ 4.0	0.25- ≥ 4.0
Osteomyelitis/Bone³					
<i>Staphylococcus aureus</i>	20	0.5	0.5	0.5	0.5 ⁴
<i>Staphylococcus intermedius</i>	15	0.5	≥ 4.0	≥ 4.0	0.25- ≥ 4.0
<i>Staphylococcus</i> spp.	18	0.5	≥ 4.0	≥ 4.0	0.25- ≥ 4.0
Beta-hemolytic streptococci	21	0.5	2.0	2.0	0.25- ≥ 4.0
<i>Streptococcus</i> spp.	21	≥ 4.0	≥ 4.0	≥ 4.0	0.25- ≥ 4.0
Dermal/Skin⁵					
<i>Staphylococcus aureus</i>	25	0.5	≥ 4.0	≥ 4.0	0.25- ≥ 4.0
<i>Staphylococcus intermedius</i>	48	0.5	≥ 4.0	≥ 4.0	0.125- ≥ 4.0
<i>Staphylococcus</i> spp.	32	0.5	≥ 4.0	≥ 4.0	0.25- ≥ 4.0
Beta-hemolytic streptococci	17	0.5	0.5	0.5	0.25-0.5

- The correlation between the *in vitro* susceptibility data and clinical response has not been determined.
- Soft Tissue/Wound: Includes samples labeled wound, abscess, aspirate, exudates, draining tract, lesion, and mass
- Osteomyelitis/Bone: includes samples labeled bone, fracture, joint, tendon
- No range, all isolates yielded the same value
- Dermal/Skin: Includes samples labeled skin, skin swab, biopsy, incision, lip

Antirobe
brand of clindamycin hydrochloride capsules, USP
Antirobe Aquadrops
brand of clindamycin hydrochloride liquid

Table 2. Clindamycin MIC Values ($\mu\text{g/mL}$) from Diagnostic Laboratory Survey Data Evaluating Feline Pathogens from Wound and Abscess Samples in the U.S. during 1998¹

Organism	Number of Isolates	MIC ₅₀	MIC ₉₀	Range
Bacteroides/Prevotella				
	30	0.06	4.0	≤ 0.015 -4.0
Fusobacterium spp.				
	17	0.25	0.25	≤ 0.015 -0.5
Peptostreptococcus spp.				
	18	0.13	0.5	≤ 0.015 -8.0
Porphyromonas spp.				
	13	0.06	0.25	≤ 0.015 -8.0

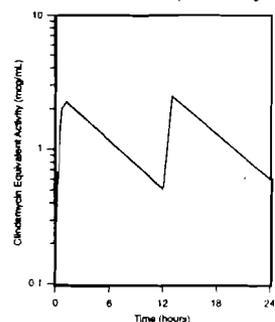
¹ The correlation between the *in vitro* susceptibility data and clinical response has not been determined.

PHARMACOLOGY

Absorption: Clindamycin hydrochloride is rapidly absorbed from the canine and feline gastrointestinal tract.

Dog Serum Levels: Serum levels at or above 0.5 $\mu\text{g/mL}$ can be maintained by oral dosing at a rate of 2.5 mg/lb of clindamycin hydrochloride every 12 hours. This same study revealed that average peak serum concentrations of clindamycin occur 1 hour and 15 minutes after oral dosing. The elimination half-life for clindamycin in dog serum was approximately 5 hours. There was no bioactivity accumulation after a regimen of multiple oral doses in healthy dogs.

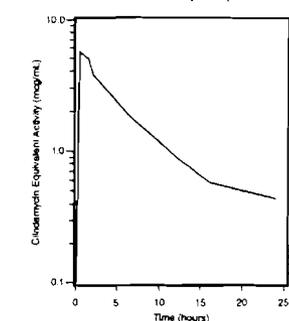
Clindamycin Serum Concentrations
2.5 mg/lb (5.5 mg/kg) After B.I.D. Oral
Dose of Antirobe Capsules to Dogs



Antirobe
brand of clindamycin hydrochloride capsules, USP
Antirobe Aquadrops
brand of clindamycin hydrochloride liquid

Cat Serum Levels: Serum levels at or above 0.5 $\mu\text{g/mL}$ can be maintained by oral dosing at a rate of 5 mg/lb of clindamycin hydrochloride liquid every 24 hours. The average peak serum concentration of clindamycin occurs approximately 1 hour after oral dosing. The elimination half-life of clindamycin in feline serum is approximately 7.5 hours. In healthy cats, minimal accumulation occurs after multiple oral doses of clindamycin hydrochloride, and steady-state should be achieved by the third dose.

Clindamycin Serum Concentrations
5 mg/lb (11 mg/kg) After Single Oral
Dose of Antirobe Aquadrops to Cats



METABOLISM AND EXCRETION

Extensive studies of the metabolism and excretion of clindamycin hydrochloride administered orally in animals and humans have shown that unchanged drug and bioactive and bioinactive metabolites are excreted in urine and feces. Almost all of the bioactivity detected in serum after ANTIROBE product administration is due to the parent molecule (clindamycin). Urine bioactivity, however, reflects a mixture of clindamycin and active metabolites, especially N-dimethyl clindamycin and clindamycin sulfoxide.

ANIMAL SAFETY SUMMARY

Rat and Dog Data: One year oral toxicity studies in rats and dogs at doses of 30, 100 and 300 mg/kg/day (13.6, 45.5 and 136.4 mg/lb/day) have shown clindamycin hydrochloride capsules to be well tolerated. Differences did not occur in the

Antirobe
clindamycin hydrochloride
capsules, USP
Antirobe Aquadrops
clindamycin
hydrochloride liquid



Antirobe
clindamycin hydrochloride
capsules, USP
Antirobe Aquadrops
clindamycin
hydrochloride liquid

Antirobe®

brand of clindamycin hydrochloride capsules, USP

Antirobe Aquadrops®

brand of clindamycin hydrochloride liquid

parameters evaluated to assess toxicity when comparing groups of treated animals with contemporary controls. Rats administered clindamycin hydrochloride at 600 mg/kg/day (272.7 mg/lb/day) for six months tolerated the drug well; however, dogs orally dosed at 600 mg/kg/day (272.7 mg/lb/day) vomited, had anorexia, and subsequently lost weight. At necropsy these dogs had erosive gastritis and focal areas of necrosis of the mucosa of the gall bladder.

Safety in gestating bitches or breeding males has not been established.

Cat Data: The recommended daily therapeutic dose range for clindamycin hydrochloride (ANTIROBE AQUADROPS Liquid) is 11 to 33 mg/kg/day (5 to 15 mg/lb/day) depending on the severity of the condition. Clindamycin hydrochloride (ANTIROBE AQUADROPS Liquid) was tolerated with little evidence of toxicity in domestic shorthair cats when administered orally at 10x the minimum recommended therapeutic daily dose (11 mg/kg; 5 mg/lb) for 15 days, and at doses up to 5x the minimum recommended therapeutic dose for 42 days. Gastrointestinal tract upset (soft feces to diarrhea) occurred in control and treated cats with emesis occurring at doses 3x or greater than the minimum recommended therapeutic dose (11 mg/kg/day; 5 mg/lb/day). Lymphocytic inflammation of the gallbladder was noted in a greater number of treated cats at the 110 mg/kg/day (50 mg/lb/day) dose level than for control cats. No other effects were noted. Safety in gestating queens or breeding male cats has not been established.

INDICATIONS

ANTIROBE (brand of clindamycin hydrochloride) Capsules (for use in dogs only) and AQUADROPS Liquid (for use in dogs and cats) are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

Dogs: Skin infections (wounds and abscesses) due to coagulase positive staphylococci (*Staphylococcus aureus* or *Staphylococcus intermedius*). **Deep wounds and abscesses** due to *Bacteroides fragilis*, *Prevotella melaninogenicus*, *Fusobacterium*

Antirobe

brand of clindamycin hydrochloride capsules, USP

Antirobe Aquadrops

brand of clindamycin hydrochloride liquid

necrophorum and *Clostridium perfringens*. **Dental infections** due to *Staphylococcus aureus*, *Bacteroides fragilis*, *Prevotella melaninogenicus*, *Fusobacterium necrophorum* and *Clostridium perfringens*. **Osteomyelitis** due to *Staphylococcus aureus*, *Bacteroides fragilis*, *Prevotella melaninogenicus*, *Fusobacterium necrophorum* and *Clostridium perfringens*.

Cats: Skin infections (wounds and abscesses) due to *Staphylococcus aureus*, *Staphylococcus intermedius*, *Streptococcus* spp., *Clostridium perfringens* and *Bacteroides fragilis*.

Dental infections due to *Staphylococcus aureus*, *Staphylococcus intermedius*, *Streptococcus* spp., *Clostridium perfringens* and *Bacteroides fragilis*.

CONTRAINDICATIONS

ANTIROBE Capsules and ANTIROBE AQUADROPS Liquid are contraindicated in animals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

Because of potential adverse gastrointestinal effects, do not administer to rabbits, hamsters, guinea pigs, horses, chinchillas or ruminating animals.

WARNINGS

Keep out of reach of children. Not for human use.

PRECAUTIONS

During prolonged therapy of one month or greater, periodic liver and kidney function tests and blood counts should be performed.

The use of ANTIROBE occasionally results in overgrowth of non-susceptible organisms such as clostridia and yeasts. Therefore, the administration of ANTIROBE should be avoided in those species sensitive to the gastrointestinal effects of clindamycin (see **CONTRAINDICATIONS**). Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy.

Clindamycin hydrochloride has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ANTIROBE should be used with caution in animals receiving such agents.

Safety in gestating bitches and queens or breeding male dogs and cats has not been established.

ADVERSE REACTIONS

Side effects occasionally observed in either clinical trials or during clinical use were vomiting and diarrhea.

To report adverse reactions or a suspected adverse reaction call 1-800-793-0596.

Antirobe

brand of clindamycin hydrochloride capsules, USP

Antirobe Aquadrops

brand of clindamycin hydrochloride liquid

DOSAGE AND ADMINISTRATION

Dogs:

Infected Wounds, Abscesses, and Dental Infections

Oral: 2.5-15.0 mg/lb body weight every 12 hours.

Duration: Treatment with ANTIROBE products may be continued up to a maximum of 28 days if clinical judgment indicates. Treatment of acute infections should not be continued for more than three or four days if no response to therapy is seen.

Dosage Schedule:

Capsules

ANTIROBE 25 mg, administer 1-6 capsules every 12 hours for each 10 pounds of body weight.

ANTIROBE 75 mg, administer 1-6 capsules every 12 hours for each 30 pounds of body weight.

ANTIROBE 150 mg, administer 1-6 capsules every 12 hours for each 60 pounds of body weight.

ANTIROBE 300 mg, administer 1-6 capsules every 12 hours for each 120 pounds of body weight.

Liquid

ANTIROBE AQUADROPS, administer 1-6 mL/10 lbs body weight every 12 hours.

Dogs:

Osteomyelitis

Oral: 5.0-15.0 mg/lb body weight every 12 hours

Duration: Treatment with ANTIROBE is recommended for a minimum of 28 days. Treatment should not be continued for longer than 28 days if no response to therapy is seen.

Dosage Schedule:

Capsules

ANTIROBE 25 mg, administer 2-6 capsules every 12 hours for each 10 pounds of body weight.

ANTIROBE 75 mg, administer 2-6 capsules every 12 hours for each 30 pounds of body weight.

ANTIROBE 150 mg, administer 2-6 capsules every 12 hours for each 60 pounds of body weight.

ANTIROBE 300 mg, administer 2-6 capsules every 12 hours for each 120 pounds of body weight.

Liquid

ANTIROBE AQUADROPS, administer 2-6 mL/10 lbs body weight every 12 hours.

Cats:

Infected Wounds, Abscesses, and Dental Infections

5.0 - 15.0 mg/lb body weight once every 24 hours depending on the severity of the condition.

Duration: Treatment with ANTIROBE AQUADROPS Liquid may be continued up to a

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brand of clindamycin hydrochloride capsules, USP

Antirobe Aquadrops

brand of clindamycin hydrochloride liquid

maximum of 14 days if clinical judgment indicates. Treatment of acute infections should not be continued for more than three to four days if no clinical response to therapy is seen.

Dosage Schedule:

ANTIROBE AQUADROPS, to provide 5.0 mg/lb, administer 1 mL/5 lbs body weight once every 24 hours; to provide 15.0 mg/lb, administer 3 mL/5 lbs body weight once every 24 hours.

HOW SUPPLIED

ANTIROBE Capsules are available as:

25 mg - bottles of 600NDC 0009-3043-01

75 mg - bottles of 200NDC 0009-3044-01

150 mg - bottles of 100NDC 0009-3045-01

150 mg - blister packages

of 100NDC 0009-3045-08

300 mg - blister packages

of 100NDC 0009-5015-01

NADA #120-161, Approved by FDA

ANTIROBE AQUADROPS Liquid is available as 20 mL filled in 30 mL bottles (25 mg/mL) supplied in packers containing 12 cartoned bottles with direction labels and calibrated dosing droppers, NDC 0009-3179-01. NADA #135-940, Approved by FDA

To report a suspected adverse reaction or to request a material safety data sheet (MSDS), call 1-800-793-0596.

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

ANTIROBE AQUADROPS

Made by

Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

ANTIROBE Capsules

Made in Canada for

Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

By **Patheon YM Inc.**

Don Mills, Ontario, M3B 1Y5
CANADA

Revised February 2002

813 805 711E

692074

3179-01-000

Approved for use in dogs.

Recommended dosage:

For therapy of wounds, abscesses, and dental infections, 1-6 capsules for each 10 pounds body weight every 12 hours.

For therapy of osteomyelitis, 2-6 capsules for each 10 pounds body weight every 12 hours.

See package insert for complete product information.

Warning—Keep out of reach of children. Not for human use. Keep container tightly closed.

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

Each capsule contains:

Clindamycin hydrochloride equivalent to clindamycin, 25 mg.

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5719-25/2

NDC 0009-3043-01
600 Capsules

Antirobe®
Capsules

clindamycin hydrochloride
capsules, USP

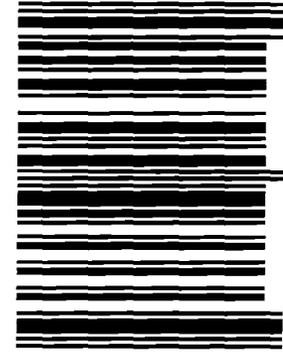
25 mg

Equiv. to 25 mg clindamycin

For Use in Dogs Only

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

NADA #120-161, Approved by FDA



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Approved for use in dogs.

Recommended dosage:

For therapy of wounds, abscesses, and dental infections, 1-6 capsules for each 30 pounds body weight every 12 hours. For therapy of osteomyelitis, 2-6 capsules for each 30 pounds body weight every 12 hours.

See package insert for complete product information.

Warning—Keep out of reach of children.

Not for human use.

Keep container tightly closed.

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

Each capsule contains:

Clindamycin hydrochloride equivalent to clindamycin, 75 mg.

812 765 106B

5719-26/2

NDC 0009-3044-01

200 Capsules

Antirobe[®]

Capsules

clindamycin hydrochloride capsules, USP

75 mg

Equiv. to 75 mg clindamycin

For Use in Dogs Only

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

NADA #120-161, Approved by FDA



0009-3044-01 2

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Approved for use in dogs.

Recommended dosage:

For therapy of wounds, abscesses, and dental infections, 1-6 capsules for each 60 pounds body weight every 12 hours.

For therapy of osteomyelitis, 2-6 capsules for each 60 pounds body weight every 12 hours.

See package insert for complete product information.

Warning—Keep out of reach of children. Not for human use.

Keep container tightly closed.

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

Each capsule contains:

Clindamycin hydrochloride equivalent to clindamycin, 150 mg.

812 774 106B
5719-21/2

NDC 0009-3045-01

100 Capsules

Antirobe[®]

Capsules

clindamycin hydrochloride
capsules, USP

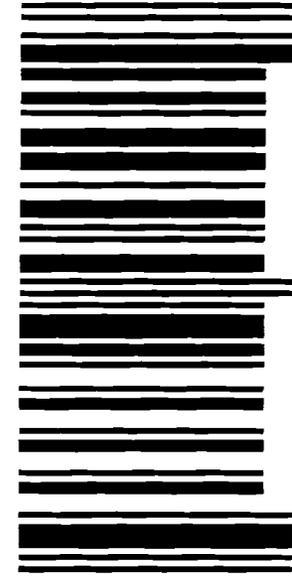
150 mg

Equiv. to 150 mg clindamycin

For Use in Dogs Only

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

NADA #120-161, Approved by FDA



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