Approval Date: December 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.

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:	CLINDAROBE 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: CLINDAROBE 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 CLINDAROBE 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	CLINDAROBE Mean	ANTIROBE Mean	Lower Bound	Upper Bound
AUC (μg*hr/mL)	22842.9.8*	20669.3*	99.6%	122.7%
C_{MAX} (μg/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 f2 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 CLINDAROBE 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:
CLINDAROBE 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