

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-780

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
DIVISION OF PHARMACEUTICAL EVALUATION I

NDA 21-780/N000 S001 BM000	SUBMISSION DATE June 16, 2004 August 6, 2004 December 20, 2004
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TYPE: ORIGINAL NEW DRUG APPLICATION

BRAND NAME: Nitro Mist® Lingual Spray
GENERIC NAME: Nitroglycerin Aerosol Lingual Spray
DOSAGE STRENGTH: 0.4 mg/activation, 15 ml (dose size), aerosol lingual spray
INDICATION: Acute relief or prophylaxis of Angina Pectoris due to CAD

SPONSOR: Novadel Pharma, Inc.
 Flemington, NJ

PRIMARY REVIEWER: Lydia Velazquez, Pharm.D.
TEAM LEADER: Patrick Marroum, Ph.D.
 Nhi Beasley, Pharm.D.

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Executive Summary

Novadel Pharma, Inc. is seeking approval of nitroglycerin oral lingual spray for the treatment of acute relief or prophylaxis of Angina Pectoris due to coronary artery disease. Nitroglycerin is an organic nitrate that is a vasodilator; which affects arterial and venous beds. The submitted NDA application is for an aerosol lingual spray that is to be taken orally when needed for acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease. It is designed to deliver 0.4 mg of nitroglycerin in the form of droplets spray. The sponsor has submitted their own clinical trial, literature reports, and a descriptive pharmacokinetic study with respect to safety and efficacy from other nitroglycerin products. The pharmacokinetic study is descriptive in nature in order to characterize the pharmacokinetics of their product.

Section 6 of NDA 21-780 includes 1 study that is a descriptive pharmacokinetics. It involved a single-dose bioavailability and pharmacokinetic study characterizing the pharmacokinetics of trinitroglycerin as well as its active metabolites, 1,2- and 1,3-dinitroglycerin. The results as illustrated bellow:

Pharmacokinetic Parameters for GTN, 1,2-GDN, and 1,3-GDN (Arithmetic Means \pm Standard Deviation)						
Analytes	AUC _{0-T} (ng \cdot min/mL)	AUC _{0-inf} (ng \cdot min/mL)	C _{max} (ng/mL)	T _{max} (min)	K _e (L/min)	T _{1/2} (min)
GTN	9.157 \pm 7.37	7.278 \pm 5.84 ^a	0.823 \pm 0.692	8.25 \pm 3.519	0.1464 \pm 0.0431 ^a	5.161 \pm 1.638 ^a
1,2-GDN	284.4 \pm 41.57	304.6 \pm 47.44	3.722 \pm 0.979	33.67 \pm 21.18	0.01763 \pm .0021	39.82 \pm 4.65
1,3-GDN	78.85 \pm 13.70	84.82 \pm 15.54	0.987 \pm 0.278	40.58 \pm 20.00	0.0176 \pm .0022	40.01 \pm 5.058

AUC_{0-inf}=area under the time-concentration curve from Time 0 to infinity; AUC_{0-T}=area under the time-concentration curve from Time 0 to time of last measurement; C_{max}=maximum concentration; GDN=dinitroglycerin; GTN=nitroglycerin; K_e=elimination rate constant; T_{max}=time to maximum concentration; t_{1/2}=elimination half-life.

Note: All parameters were calculated from data on 12 subjects, except as noted otherwise.

^a n=10

The sponsor also submitted pharmacokinetic information from other formulations in the literature in order to demonstrate that the pharmacokinetics of their product is similar to what is already out in the market. The sponsor claims that their comparison indicates that Novadel Pharma's product is within the parameters of the results reported in the literature for other nitroglycerin formulations. However, this comparison does not demonstrate bioequivalence between Novadel Pharma's formulation and any other product reported.

Study reports submitted include two drug interaction studies involving coadministration of tissue-type plasminogen activator (t-PA) and GTN resulting in decreases in the thrombolytic effect of t-PA. One of those studies was reviewed and the other was not due to redundancy of information. The sponsor did propose additional verbage in the PRECAUTIONS section of the labeling, specifically to drug interactions between aspirin (ASA) and dihydroergotamine (DHE). However, no literature reports were submitted

for review and verification. As a result, a literature search was performed by the Agency in hopes of data verification. One study was found for the DHE drug interaction claim that did in fact verify the sponsor's claim in the labeling of coadministration resulting in a decrease in the first-pass metabolism of DHE and subsequent increases in the bioavailability (BA) up to 370%. Two articles were discovered for the ASA/GTN interaction and one was reviewed since similar information was found in both. Increases in GTN C_{max} (67%) and AUC (73%) were observed after single dose (SD) ASA treatment coadministered with GTN. Enhanced changes in physiological parameters (heart rate increase of 8%, decrease in diastolic arterial pressure of 6%, decrease in end systolic diameter of 17%, and a decrease in end diastolic diameter of 14%) were observed as well. The multiple dose (MD) ASA treatment resulted in an increase in AUC of 39% with GTN coadministered and minimal changes in physiological parameters (heart rate increase of 2%, decrease in diastolic arterial pressure of 6%, decrease in end systolic diameter of 17%, and a decrease in end diastolic diameter of 14%) were found.

The assay used to quantify Trinitroglycerin, 1,2-Dinitroglycerin, and 1,3-Dinitroglycerin is a validated GC assay with MS detection and was sensitive, precise, and accurate. The limit of quantification of Trinitroglycerin in plasma is 0.005 ng/mL and 0.05 ng/mL for 1,2- and 1,3-Dinitroglycerin.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-780 submitted on June 17 and August 6, 2004; for NitroMist® aerosol lingual spray and finds the clinical pharmacology and biopharmaceutics section acceptable. However, the following labeling recommendations should be addressed by the sponsor:

REVIEWER COMMENTS TO THE SPONSOR:

The following Labeling Comments should be addressed by the sponsor:

LABELING

- I. The "CLINICAL PHARMACOLOGY", "Pharmacokinetics and Drug Absorption" section of the proposed labeling should be modified as follows below in order to provide the reader values by which an assessment and a true comparison can be made:

Pharmacokinetics and Drug Absorption
Proposed by Sponsor:

3 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Lydia Velazquez, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. _____

And Nhi Beasley, Pharm.D. _____

OCPB Briefing was held on February 18th, 2004. Attendees were: L. Velazquez, M. Mehta, P. Marroum, and N. Stockbridge.

CC list: HFD-110: NDA 21-780 (DavidJ, StockbridgeN); HFD-860: (VelazquezL, MarroumP, BeasleyN, MehtaM, RahmanA); CDER Central Document Room

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Summary of Important CPB Findings

Novadel Pharma, Inc. is seeking approval of nitroglycerin oral lingual spray for the treatment of acute relief or prophylaxis of angina pectoris due to coronary artery disease. Nitroglycerin is an organic nitrate that is a vasodilator; which affects arterial and venous beds. The submitted NDA application is for an aerosol lingual spray that is to be taken orally as needed for the mentioned indication. It is designed to deliver 0.4 mg of nitroglycerin in the form of droplets spray. The sponsor submitted their own clinical trial, literature reports, and pharmacokinetic study for safety and efficacy findings from other nitroglycerin products. As a result, Novadel Pharma, Inc. has submitted a pharmacokinetic study that is descriptive in nature in order to characterize the pharmacokinetics of their product.

Section 6 of NDA 21-780 includes the one descriptive pharmacokinetic study previously mentioned.

The study in question is a single-dose bioavailability and pharmacokinetic study to characterize the pharmacokinetics of trinitroglycerin. The active metabolites, 1,2- and 1,3-dinitroglycerin were also characterized. At least 80% of $AUC_{0-\infty}$ was measured by AUC_{0-t} (180min). Drug concentrations were detected in plasma beginning at 2, 4, and a maximum of 8 minutes for trinitroglycerin, 1,2-dinitroglycerin, and 1,3-dinitroglycerin, respectively. Maximum concentrations ranged from 0.210 to 2.23 ng/mL for trinitroglycerin, 2.48 to 5.15 ng/mL for 1,2-dinitroglycerin, and 0.722 to 1.49 ng/mL for 1,3-dinitroglycerin. Maximum time to reach C_{max} was between 4 and 15 minutes, 15 to 90 minutes, and 20 to 90 minutes for trinitroglycerin, 1,2-dinitroglycerin, and 1,3-dinitroglycerin, respectively. additional details are listed below:

Pharmacokinetic Parameters for GTN, 1,2-GDN, and 1,3-GDN (Arithmetic Means \pm Standard Deviation)						
Analytes	AUC_{0-T} (ng \cdot min/mL)	$AUC_{0-\infty}$ (ng \cdot min/mL)	C_{max} (ng/mL)	T_{max} (min)	K_d (L/min)	T_H (min)
GTN	9.157 \pm 7.37	7.278 \pm 5.84 ^a	0.823 \pm 0.692	8.25 \pm 3.519	0.1464 \pm 0.0431 ^a	5.161 \pm 1.638 ^a
1,2-GDN	284.4 \pm 41.57	304.6 \pm 47.44	3.722 \pm 0.979	33.67 \pm 21.18	0.01763 \pm .0021	39.82 \pm 4.65
1,3-GDN	78.85 \pm 13.70	84.82 \pm 15.54	0.987 \pm 0.278	40.58 \pm 20.00	0.0176 \pm .0022	40.01 \pm 5.058

$AUC_{0-\infty}$ =area under the time-concentration curve from Time 0 to infinity; AUC_{0-T} =area under the time-concentration curve from Time 0 to time of last measurement; C_{max} =maximum concentration; GDN=dinitroglycerin; GTN=nitroglycerin; K_d =elimination rate constant; T_{max} =time to maximum concentration; t_H =elimination half-life.

Note: All parameters were calculated from data on 12 subjects, except as noted otherwise.

^a n=10

The sponsor also submitted pharmacokinetic information from other formulations in the form of literature reports in order to demonstrate that the pharmacokinetics of their product are similar to what is already out in the market. The sponsor claims that the anecdotal comparison indicates that Novadel Pharma's product is within the parameters of the results reported in the literature for other nitroglycerin formulations.

Study reports submitted include two drug interaction studies involving coadministration of tissue-type plasminogen activator (t-PA) and GTN resulting in decreases in the thrombolytic effect of t-PA. One of those studies was reviewed and the other was not due to redundancy of information. The sponsor did propose additional verbiage in the PRECAUTIONS section of the labeling, specifically to drug interactions between aspirin (ASA) and dihydroergotamine (DHE). However, no literature reports were submitted for review and verification. As a result, a literature search was performed by the Agency in hopes of data verification. One study was found for the DHE drug interaction claim that did in fact verify the sponsor's claim in the labeling of coadministration resulting in a decrease in the first-pass metabolism of DHE and subsequent increases in the BA up to 370%. A study involving the possible interaction between ASA and GTN was performed resulting in increases in GTN C_{max} (67%) and AUC (73%) after SD ASA treatment coadministered with GTN. Enhanced changes in physiological parameters (heart rate increase of 8%, decrease in diastolic arterial pressure of 6%, decrease in end systolic diameter of 17%, and a decrease in end diastolic diameter of 14%) were observed as well. MD ASA treatment resulted in an increase in AUC of 39% with GTN coadministered and minimal changes in physiological parameters (heart rate increase of 2%, decrease in diastolic arterial pressure of 6%, decrease in end systolic diameter of 17%, and a decrease in end diastolic diameter of 14%).

The assay used to quantify Trinitroglycerin, 1,2-Dinitroglycerin, and 1,3-Dinitroglycerin is a validated GC assay with MS detection and was sensitive, precise, and accurate. The limit of quantification of Trinitroglycerin in plasma is 0.005 ng/mL and 0.05 ng/mL for 1,2- and 1,3-Dinitroglycerin.

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QUESTION BASED REVIEW

I. INTRODUCTION

- A. WHAT ARE THE HIGHLIGHTS OF THE CHEMISTRY, FORMULATION AND PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG AND DRUG PRODUCT?

FORMULATION AND MANUFACTURING

Nitroglycerin lingual spray is to be marketed as a pump spray to deliver 0.4 mg per spray for lingual administration. Below is a table summarizing the composition of the "to be marketed" product:

Ratio of Components (w:w)	Components	Composition	Dose Container (mg/actuation)
1	GTN Solution	GTN	0.4
		^a	
		peppermint oil	
		L(-) menthol	
2	Propellant	n-butane	0.4
		Total per actuation	0.4
	Bottle	Typical glass	15 mL
	Valve	metered dose	0.4

GTN=nitroglycerin; w:w=weight:weight ratio.

^a caprylic/capric diglycerol succinate

- B. WHAT IS THE PROPOSED MECHANISM OF ACTION AND THERAPEUTIC INDICATIONS?

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins with more prominent effects on the veins. Dilation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load).

The mechanism by which nitroglycerin relieves angina pectoris is believed to be by a decrease in myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) by both the arterial and venous effects of nitroglycerin resulting in a more favorable supply-demand ratio.

While the large epicardial coronary arteries are also dilated by nitroglycerin, the extent to which this action contributes to relief of exertional angina is unclear.

Nitroglycerin is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

C. WHAT IS THE PROPOSED DOSAGE AND ADMINISTRATION?

Nitroglycerin lingual spray is to be taken via the lingual route as needed for acute relief or prophylaxis of angina pectoris due to coronary artery disease. It is designed to deliver 0.4 mg of nitroglycerin in the form of droplets spray.

II. CLINICAL PHARMACOLOGY

A. WAS THE PHARMACOKINETICS OF TRINITROGLYCERIN CHARACTERIZED ADEQUATELY?

The pharmacokinetics of trinitroglycerin and its metabolites were characterized in a pharmacokinetic study. Results are illustrated below:

Pharmacokinetic Parameters for GTN, 1,2-GDN, and 1,3-GDN						
(Arithmetic Means \pm Standard Deviation)						
Analytes	AUC_{0-T} (ng\cdotmin/mL)	AUC_{0-Inf} (ng\cdotmin/mL)	C_{max} (ng/mL)	T_{max} (min)	K_e (L/min)	T_{1/2} (min)
GTN	9.157 \pm 7.37	7.278 \pm 5.84 ^a	0.823 \pm 0.692	8.25 \pm 3.519	0.1464 \pm 0.0431 ^a	5.161 \pm 1.638 ^a
1,2-GDN	284.4 \pm 41.57	304.6 \pm 47.44	3.722 \pm 0.979	33.67 \pm 21.18	0.01763 \pm .0021	39.82 \pm 4.65
1,3-GDN	78.85 \pm 13.70	84.82 \pm 15.54	0.987 \pm 0.278	40.58 \pm 20.00	0.0176 \pm .0022	40.01 \pm 5.058

AUC_{0-Inf}=area under the time-concentration curve from Time 0 to infinity; AUC_{0-T}=area under the time-concentration curve from Time 0 to time of last measurement; C_{max}=maximum concentration; GDN=dinitroglycerin; GTN=trinitroglycerin; K_e=elimination rate constant; T_{max}=time to maximum concentration; t_{1/2}=elimination half-life.

Note: All parameters were calculated from data on 12 subjects, except as noted otherwise.

^a n=10

B. WERE THE CORRECT MOIETIES IDENTIFIED AND PROPERLY MEASURED TO ASSESS CLINICAL PHARMACOLOGY?

Trinitroglycerin was quantified in plasma. Its active metabolites, 1,2- and 1,3-dinitroglycerin were also characterized.

ASSAY VALIDATION

The assay used to quantify Trinitroglycerin, 1,2-Dinitroglycerin, and 1,3-Dinitroglycerin is a validated GC assay with MS detection and was sensitive, precise, and accurate. The limit of quantification of Trinitroglycerin in plasma is 0.005 ng/mL and 0.05 ng/mL for 1,2- and 1,3-Dinitroglycerin.

C. WERE ANY DRUG INTERACTIONS EXPLORED?

A drug interaction study involving coadministration of t-PA with GTN resulted in significant decreases in plasma t-PA antigen concentrations and impairment of the thrombolytic effect of t-PA in acute MI patients.

	Group 1 (n = 11)	Group 2 (n = 36)
Clinical Variables		
Age (years)	69 ± 3*	61 ± 2
Sex (men vs women)	10/1	33/3
Site of myocardial infarction (anterior vs inferior)	5/6	18/18
Time from symptom onset to t-PA administration (min)	109 ± 12	123 ± 17
Mean arterial pressure (mm Hg)	96 ± 6	105 ± 4
Previous angina or myocardial infarction (%)	63	64
Chest pain at the beginning of thrombolytic treatment (%)	100	100
Predicted infarct size (%)	20 ± 3	23 ± 1
Laboratory data		
Plasma t-PA antigen baseline (ng/ml)	9 ± 2	12 ± 2
Plasma t-PA antigen and t-PA infusion (ng/ml)	932 ± 207†	423 ± 66
Plasma t-PA antigen 1 hour after t-PA infusion (ng/ml)	353 ± 72†	153 ± 76
Plasma t-PA antigen 6 hours after t-PA infusion (ng/ml)	150 ± 26†	30 ± 19
Plasma PAI-1 antigen baseline (ng/ml)	26 ± 4	32 ± 2
Plasma PAI-1 antigen and t-PA infusion (ng/ml)	22 ± 3	34 ± 2
Plasma PAI-1 antigen 1 hour after t-PA infusion (ng/ml)	25 ± 3‡	37 ± 2
Plasma PAI-1 antigen 6 hours after t-PA infusion (ng/ml)	26 ± 3	36 ± 2

*p < 0.02 versus group 2; †p < 0.005 versus group 2; ‡p < 0.05 versus group 2.
 Data are expressed as mean ± SEM.
 PAI-1 = plasminogen activator type-1 inhibitor; t-PA = tissue-type plasminogen activator.

A study between GTN and DHE was performed in six immunocompromised patients that were taking DHE for their hypotension. Coadministration of GTN resulted in DHE increases in BA ranging from 56% to 370%; but no alteration in the absorption was observed. SBP increased 27% (p<0.05) two hours post DHE administration (same dose as previously taken alone) when taken with GTN.

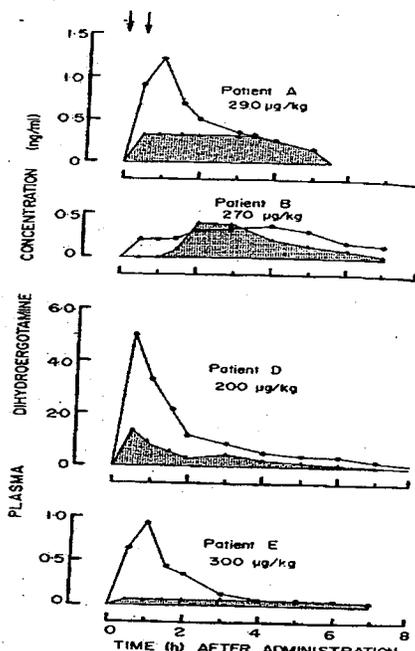


Fig. 1 Effect of oral glyceryl trinitrate on plasma DHE concentrations after oral doses. Triangles represent plasma concentrations after DHE alone and circles after DHE with glyceryl trinitrate. Arrows represent the times at which 600-µg oral doses of glyceryl trinitrate were taken.

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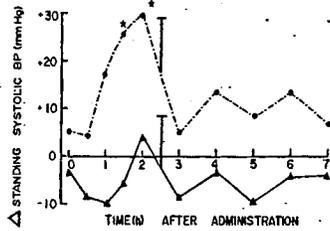


Fig. 2. Changes from placebo in standing systolic blood pressure ($\bar{x} \pm \text{SEM}$) after oral DHE with oral glyceryl trinitrate (*) and without glyceryl trinitrate (Δ) in four patients. * $P < 0.05$.

Increases in GTN C_{max} (67%) and AUC (73%) were observed after SD ASA treatment (C) coadministered with GTN. Enhanced changes in physiological parameters (heart rate increase of 8%, decrease in diastolic arterial pressure of 6%, decrease in end systolic diameter of 17%, and a decrease in end diastolic diameter of 14%) were observed as well. MD ASA treatment (B) resulted in an increase in AUC of 39% with GTN with minimal changes in physiological parameters (heart rate increase of 2%, decrease in diastolic arterial pressure of 6%, decrease in end systolic diameter of 17%, and a decrease in end diastolic diameter of 14%).

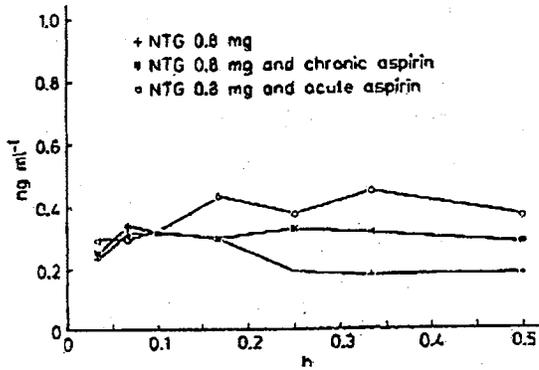


Fig. 1. Mean plasma level curves in the three treatment groups. A NTG 0.8 mg - + B NTG 0.8 mg and chronic aspirin - * C NTG 0.8 mg and acute aspirin - o

Mean haemodynamic parameters before and during 30 min after NTG administration				
	Heart Rate (beats·min ⁻¹)	DAF (mmHg)	ESD (mm)	EDD (mm)
Control	73.7 ± 12.6	66 ± 6.6	35.5 ± 3.2	33 ± 10
Treatment A (NTG)	77 ± 11	64 ± 9	35 ± 10	49 ± 10
Treatment B (NTG + analgesic dosage)	75 ± 11	61 ± 11	32 ± 6	46 ± 6 ^a
Treatment C (NTG + analgesic dosage)	83 ± 17 ^a	60 ± 8 ^a	29 ± 5 ^a	42 ± 6 ^a

^a $p < 0.05$; ^b $p < 0.001$

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III. BIOPHARMACEUTICS

A. IS THE PROPOSED LABELING FOR NITROGLYCERIN LINGUAL SPRAY ACCEPTABLE?

The proposed labeling for Nitroglycerin lingual spray is acceptable provided the Reviewer Labeling Comments described in the Recommendations section are addressed by the sponsor.

A copy of the proposed package insert is included in Appendix I.

Appendix I
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DETAILED LABELING RECOMMENDATIONS

Appendix E
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✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

**Appendix I:
Proposed Package Insert**

Appendix I
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 § 552(b)(5) Deliberative Process

**Appendix II:
Individual Review of Pharmacokinetic Study**

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STUDY FPC 99-003 – A PILOT PHARMACOKINETIC STUDY OF NITROGLYCERIN LINGUAL SPRAY (0.4 MG/ACTIVATION) UNDER FASTING CONDITIONS.

STUDY INVESTIGATOR AND SITE:

REPORT # FPC 99-003

VOLUMES 1.7 TO 1.9

STUDY DATES: June 22 - 23, 2002

OBJECTIVES:

To determine the bioavailability (rate and extent of absorption) of a single dose of nitroglycerin delivered as a lingual spray, under fasting conditions.

FORMULATION:

Nitroglycerin 0.4 mg/activation, 15 mL (dose size), aerosol lingual spray, Fleming Pharmaceutical Corp. (Lot No. GTN-004, Exp Date: not available, Manuf Date: 11/08/01)

STUDY DESIGN:

This was an open-label, single-dose, one-treatment, one-period, bioavailability and pharmacokinetic study in 12 healthy volunteers (11 males and 1 female, 11 Blacks and 1 Caucasian) under fasted conditions. The age range of the subjects was between 18 to 40 years. All were confined in the clinical facility for at least 12 hours before dosing and for at least 6 hours after dosing to obtain blood samples. Standardized meals were served with no caffeine, no grapefruit containing beverages or food, and had to be xanthine-free throughout study confinement. Smoking was not permitted from one hour prior to dosing until discharge from the clinical facility.

DRUG ADMINISTRATION:

Three dosing groups of 4 subjects per group (a 0700, 0800, and 0900 hours dosing time group) were created for ease of drug administration by the staff. Everyone received the same dose of nitroglycerin and all received one ibuprofen tablet of 2 mg within 30 minutes of their scheduled dose of nitroglycerin lingual spray. A single oral dose of nitroglycerin lingual spray was administered every two minutes three times until the full dose of 1.2 mg was given. Everyone in the study was instructed not to swallow for 5 minutes (a dry swallow was permitted) following drug administration. All subjects fasted for at least 10 hours before dosing and remained fasted until 5 hours post drug administration. Water restriction was maintained from 1 hour before through one hour post drug administration. After this time, water was permitted ad lib.

ANALYTICAL METHODS:

Plasma samples were analyzed for trinitroglycerine, 1,2 dinitro and 1,3 dinitroglycerin concentrations by a validated GC with MS detection method performed at _____

Trinitroglycerin

Linearity

The assay was linear over the measured concentration range of 0.005 to 5.00 ng/mL with $r^2 > 0.99$.

Precision

Within batch precision using area ratio methods ranged from 1.65 to 14.2%. The between batch precision was -2.29 to 12.6%.

Accuracy

The percent recovery for low, middle, and high quality control samples was 91.8%, 89.1%, and 88.3%.

Lower Limit of Quantitation (LLOQ)

The LLOQ of the assay was established at 0.005 ng/mL.

1,2-Dinitroglycerin

Linearity

The assay was linear over the measured concentration range of 0.05 to 10.0 ng/mL with $r^2 > 0.99$.

Precision

Within batch precision using area ratio methods ranged from 1.34 to 12.2%. The between batch precision was 0.519 to 9.68%.

Accuracy

The percent recovery for low, middle, and high quality control samples was 66.7%, 65.7%, and 66.3%.

Lower Limit of Quantitation (LLOQ)

The LLOQ of the assay was established at 0.05 ng/mL.

1,3-Dinitroglycerin

Linearity

The assay was linear over the measured concentration range of 0.05 to 10.0 ng/mL with $r^2 > 0.99$.

Precision

Within batch precision using area ratio methods ranged from 0.578 to 9.05%. The between batch precision was -0.613 to 8.94%.

Accuracy

The percent recovery for low, middle, and high quality control samples was 64.6%, 64.4%, and 66.3%.

Lower Limit of Quantitation (LLOQ)

The LLOQ of the assay was established at 0.05 ng/mL.

PHARMACOKINETIC SAMPLE COLLECTION:

Pharmacokinetic and statistical analyses were conducted on reported values. Plasma samples were collected at baseline (pre-dose), then at 2, 4, 6, 8, 10, 12, 15, 20, 25, 30, 45, 60, 90, 120, 150, and 180 minutes post.

Pharmacokinetic parameters calculated were C_{max} , T_{max} , elimination $T_{1/2}$, AUC_{0-t} , AUC_{0-inf} , and K_{el} .

RESULTS:

At least 80% of AUC_{0-inf} was measured by AUC_{0-t} . All information provided below will be for trinitroglycerin, 1,2-dinitroglycerin, and 1,3-dinitroglycerin, in that order. Drug concentrations were detected in plasma beginning at 2, 4, and a maximum of 8 minutes, respectively. Maximum concentrations for all ranged from 0.210 to 2.23 ng/mL for trinitroglycerin, 2.48 to 5.15 ng/mL for 1,2-dinitroglycerin, and 0.722 to 1.49 ng/mL for 1,3-dinitroglycerin. Maximum time to reach C_{max} was between 4 and 15 minutes, 15 to 90 minutes, and 20 to 90 minutes, respectively. Pharmacokinetic parameters for all three analytes are illustrated below in Tables 1 to 3.

SAFETY:

All 12 subjects completed the study. Nine of the subjects experienced at least one adverse event. A total of 16 adverse events were reported during the study. All were mild in severity. Five were assessed as being remotely related to study drug. Eleven were assessed as being study drug related and included 3 sleepiness events (1 possible, 2 probable), 5 headaches, 1 pounding in chest, 1 visual white and red flashes, and 1 disorientation (all definite).

CONCLUSIONS:

Descriptive pharmacokinetics was obtained for trinitroglycerin and its two active metabolites.

REVIEWER'S COMMENT:

1. The reviewer concurs.

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Table 1 – Pharmacokinetic Parameters for plasma Trinitroglycerin
arithmetic means ± standard deviations (N = 12)

Parameter	Test: Lingual Spray		
	N	Mean ± Std. Dev.	%CV
Ln AUC 0-T Geometric Mean ¹	12	1.9142 ± 0.8200 6.782	
Ln AUC 0-Inf Geometric Mean	10	1.7367 ± 0.7258 5.679	
Ln C _{max} Geometric Mean	12	-0.5319 ± 0.8623 0.5875	
AUC 0-T (ng·min/mL)	12	9.157 ± 7.368	80.5
AUC 0-Inf (ng·min/mL)	10	7.278 ± 5.838	80.2
C _{max} (ng/mL)	12	0.8231 ± 0.6922	84.1
T _{max} (min)	12	8.250 ± 3.519	42.7
K _{el} (1/min)	10	0.1464 ± 0.04314	29.5
T _{1/2} (min)	10	5.161 ± 1.638	31.7

¹Antilogarithm of the mean of the log transformed parameter.

Table 2 - Pharmacokinetic Parameters for plasma 1,2-Dinitroglycerin
arithmetic means ± standard deviations (N = 12)

Parameter	Test: Lingual Spray		
	N	Mean ± Std. Dev.	%CV
Ln AUC 0-T Geometric Mean ¹	12	5.6406 ± 0.1474 281.6	
Ln AUC 0-Inf Geometric Mean	12	5.7079 ± 0.1570 301.2	
Ln C _{max} Geometric Mean	12	1.2808 ± 0.2733 3.599	
AUC 0-T (ng·min/mL)	12	284.4 ± 41.57	14.6
AUC 0-Inf (ng·min/mL)	12	304.6 ± 47.44	15.6
C _{max} (ng/mL)	12	3.722 ± 0.9787	26.3
T _{max} (min)	12	33.67 ± 21.18	62.9
K _{el} (1/min)	12	0.01763 ± 0.00208	11.8
T _{1/2} (min)	12	39.82 ± 4.651	11.7

¹Antilogarithm of the mean of the log transformed parameter.

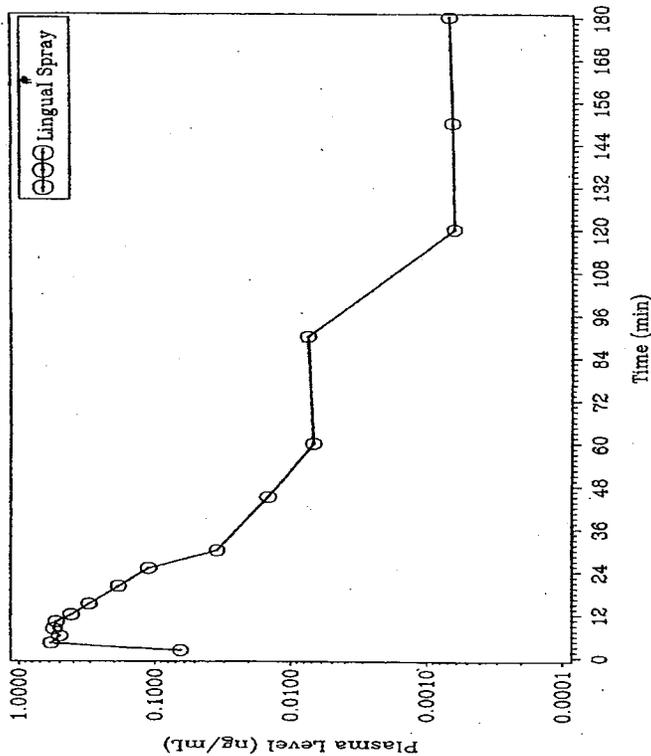
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Table 3 - Pharmacokinetic Parameters for plasma 1,3-Dinitrolycerin arithmetic means \pm standard deviations (N = 12)

Parameter	Test: Lingual Spray		
	N	Mean \pm Std. Dev.	%CV
Ln AUC 0-T Geometric Mean ¹	12	4.3537 \pm 0.1735 77.76	
Ln AUC 0-Inf Geometric Mean	12	4.4252 \pm 0.1828 83.53	
Ln Cmax Geometric Mean	12	-0.0466 \pm 0.2648 0.9544	
AUC 0-T (ng.min/mL)	12	78.85 \pm 13.70	17.4
AUC 0-inf (ng.min/mL)	12	84.82 \pm 15.54	18.3
Cmax (ng/mL)	12	0.9869 \pm 0.2779	28.2
Tmax (min)	12	40.58 \pm 20.00	49.3
Kel (1/min)	12	0.01758 \pm 0.00216	12.3
T1/2 (min)	12	40.01 \pm 5.058	12.6

¹Antilogarithm of the mean of the log transformed parameter.

Figure 1 - Mean Trinitrolycerin plasma level (Semi-log Scale), N = 12



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Figure 2 – Mean 1,2-Dinitrolycerin plasma level (Semi-log Scale), N = 12

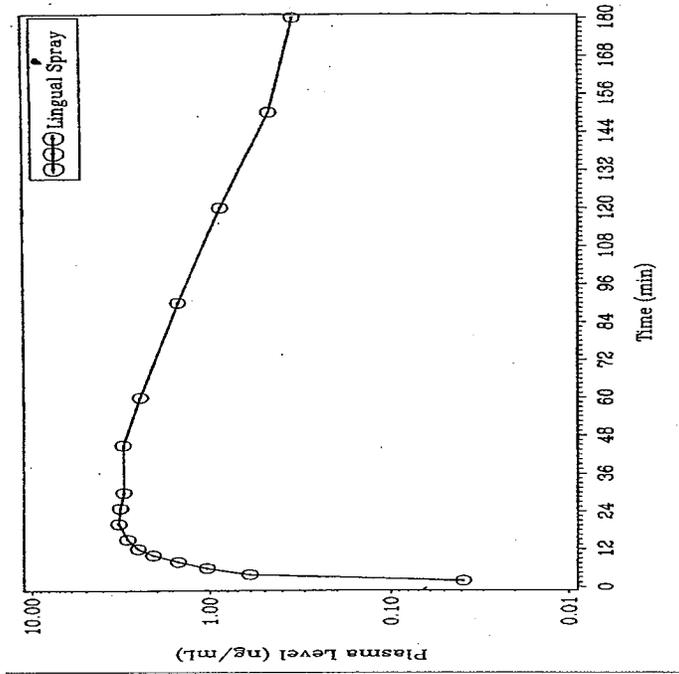
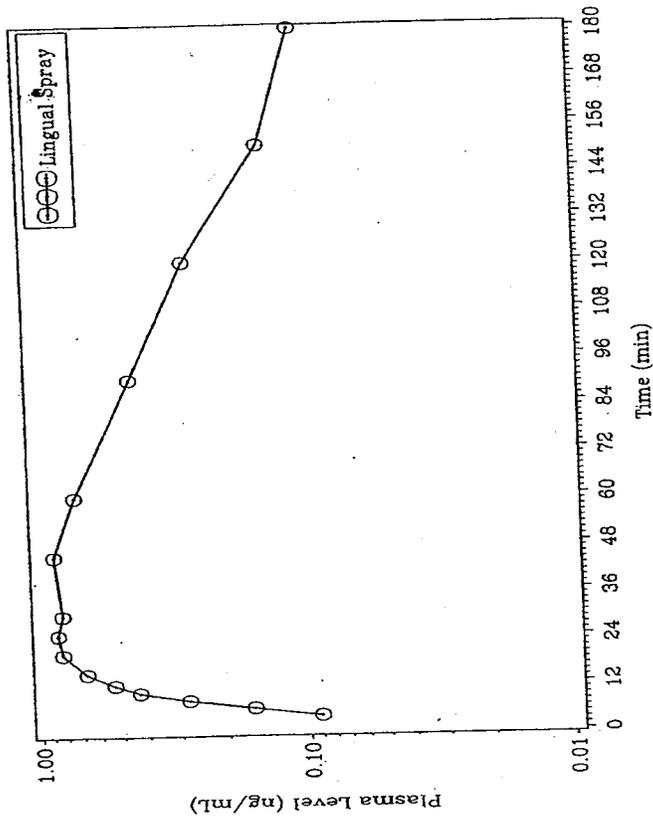


Figure 3 – Mean 1,3-Dinitrolycerin plasma level (Semi-log Scale), N = 12



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Appendix III
LITERATURE REPORTS

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Summary of Published Literature

1. CONCURRENT NITROGLYCERIN THERAPY IMPAIRS TISSUE-TYPE PLASMINOGEN ACTIVATOR (t-PA)-INDUCED THROMBOLYSIS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION. Nicolini F.A., et al., *Am J Cardiol.* 1994; 74: 662-666.

Fifty-two patients with suspected acute myocardial infarction were enrolled in order to determine if a drug interaction between t-PA and nitroglycerin exist. One group received t-PA with a saline solution (n=11) and the other group received t-PA with nitroglycerin IV (n=36) concurrently. Release of creatinine kinase occurred in 91% of patients in group 1 and 44% of patients in group 2 (GTN) as assessed by continuous ST-segment monitoring in 2 electrographic leads for stable coronary artery reperfusion (95% CI 14 to 82%, $p < 0.02$). t-PA plasma levels were greater in group 1 than the GTN group ($p < 0.005$) up to 6 hours post t-PA administration. Plasminogen activator inhibitor levels were higher in group 2. t-PA coadministered with GTN significantly decreases plasma t-PA antigen concentrations and impairs the thrombolytic effect of t-PA in acute MI patients.

	Group 1 (n = 11)	Group 2 (n = 36)
Clinical Variables		
Age (years)	69 ± 3*	61 ± 2
Sex (men vs women)	10/1	33/3
Site of myocardial infarction (anterior vs inferior)	5/6	16/16
Time from symptom onset to t-PA administration (min)	100 ± 12	123 ± 17
Mean arterial pressure (mm Hg)	98 ± 6	105 ± 4
Previous angina or myocardial infarction (%)	83	64
Chest pain at the beginning of thrombolytic treatment (%)	100	100
Predicted infarct size (%)	20 ± 3	23 ± 1
Laboratory data		
Plasma t-PA antigen baseline (ng/ml)	9 ± 2	12 ± 2
Plasma t-PA antigen end t-PA infusion (ng/ml)	332 ± 207†	423 ± 66
Plasma t-PA antigen 1 hour after t-PA infusion (ng/ml)	353 ± 72†	153 ± 76
Plasma t-PA antigen 6 hours after t-PA infusion (ng/ml)	150 ± 26†	30 ± 19
Plasma PAI-1 antigen baseline (ng/ml)	26 ± 4	32 ± 2
Plasma PAI-1 antigen end t-PA infusion (ng/ml)	22 ± 3	34 ± 2
Plasma PAI-1 antigen 1 hour after t-PA infusion (ng/ml)	25 ± 3†	37 ± 2
Plasma PAI-1 antigen 6 hours after t-PA infusion (ng/ml)	26 ± 3	35 ± 2

* $p < 0.02$ versus group 2; † $p < 0.005$ versus group 2; ‡ $p < 0.05$ versus group 2.
Data are expressed as mean ± SEM.
PAI-1 = plasminogen activator type-1 inhibitor; t-PA = tissue-type plasminogen activator.

2. LOW ORAL BIOAVAILABILITY OF DIHYDROERGOTAMINE (DHE) AND FIRST-PASS EXTRACTION IN PATIENTS WITH ORTHOSTATIC HYPOTENSION. Bobik A., et al., *Clin Pharmacol Ther.* 1981; 30: 673-679.

Six patients with autoimmune disease and orthostatic hypotension were evaluated for the relative importance of the effect of absorption and first-pass extraction on BA and the clinical effectiveness of oral DHE taken alone and with nitroglycerin. Standing SBP maximum increases occurred within 15 minutes of taking IV DHE at a dose of 10 µg/kg and after 30 minutes pressure declined in a linear fashion over the next 3 hours. DHE concentrations declined bioexponentially over time with a half-life 2.15 hours and mean CI of 862 mL/min. Upon oral administration of DHE at doses of 200 to 600 µg/kg, no rise in SBP was observed. C_{max} ranged from 0.1 to 2 ng/mL with an apparent oral absorption of 19.5 to 53.3% and minimal systemic BA variations (<0.1% to 1.5%). Coadministration of GTN resulted in DHE increases in BA ranging from 56% to 370% with no alteration in the absorption. SBP increased 27% ($p < 0.05$) two hours post DHE

administration (same dose as previously) when taken with GTN. The extent of hepatic first-pass extraction is the main determinant of the BA of DHE post oral administration and that factors that affect GI and hepatic portal vein flow such as GTN, affect its BA.

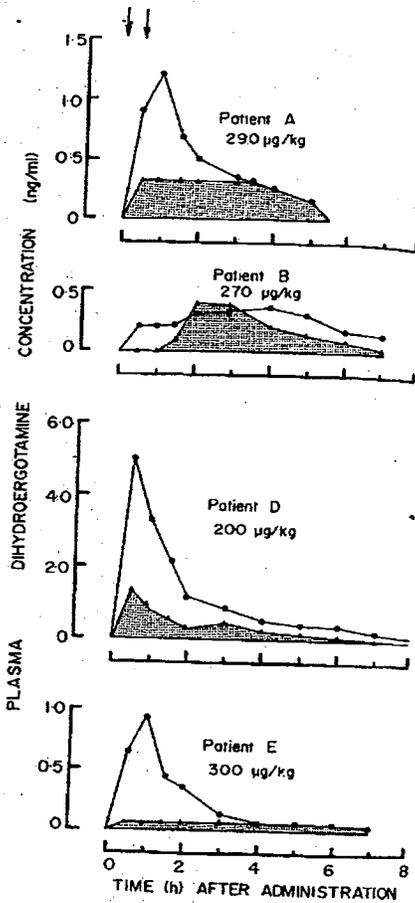


Fig. 1 Effect of oral glyceryl trinitrate on plasma DHE concentrations after oral doses. Triangles represent plasma concentrations after DHE alone and circles after DHE with glyceryl trinitrate. Arrows represent the times at which 600- μ g oral doses of glyceryl trinitrate were taken.

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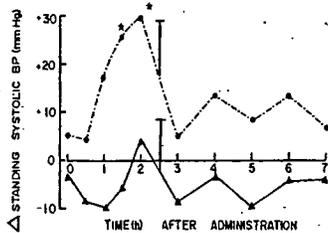


Fig. 2 Changes from placebo in standing systolic blood pressure ($\bar{x} \pm$ SEM) after oral DHE with oral glyceryl trinitrate (e) and without glyceryl trinitrate (a) in four patients. * $P < 0.05$.

3. PHARMACOLOGICAL INTERACTION BETWEEN NITROGLYCERIN AND ASPIRIN AFTER ACUTE AND CHRONIC ASPIRIN TREATMENT OF HEALTHY SUBJECTS. Rey E., et.al., *Eur J Clin Pharmacology*. 1983; 25: 779-782.

Seven healthy volunteers were enrolled in order to investigate the interaction between GTN and ASA. The rationale was to test if ASA blocks the hemodynamic response to GTN. GTN was administered at a dose of 0.8 mg (Nitrolingual spray, treatment A). ASA was given at a SD dose of 1 g (treatment C) and at MD of 0.5 g (treatment B). Increases in GTN C_{max} (67%) and AUC (73%) were observed after SD ASA treatment (C) coadministered with GTN. Enhanced changes in physiological parameters (heart rate increase of 8%, decrease in diastolic arterial pressure of 6%, decrease in end systolic diameter of 17%, and a decrease in end diastolic diameter of 14%) were observed as well. MD ASA treatment (B) resulted in an increase in AUC of 39% with GTN with minimal changes in physiological parameters (heart rate increase of 2%, decrease in diastolic arterial pressure of 6%, decrease in end systolic diameter of 17%, and a decrease in end diastolic diameter of 14%).

Table 1. Mean pharmacokinetic parameters of NTG Spray after sublingual administration of 0.8 mg dose to 7 healthy subjects in the Treatments A, B, C

Treatment	C_{max} [ng·ml ⁻¹]	t_{max} [h]	AUC ₀₋₁ [ng·ml ⁻¹ ·h]	Mean residence time [h]
A Mean	0.37	0.13	0.0991	0.225
± SD	0.15	0.056	0.0341	0.0358
B Mean	0.39	0.24	0.138	0.237
± SD	0.22	0.20	0.0980	0.0787
C Mean	0.62	0.26	0.172	0.254
± SD	0.35	0.14	0.134	0.0208

Table 2. Mean haemodynamic parameters before and during 30 min after NTG administration

	Heart Rate [beats·min ⁻¹]	DAP [mmHg]	ESD [mm]	EDD [mm]
Control	73.7 ± 12.6	66 ± 6.6	35.5 ± 3.2	35 ± 10
Treatment A (NTG)	77 ± 11	64 ± 9	35 ± 10	49 ± 10
Treatment B (NTG + antiagreg- gant dosage)	75 ± 11	61 ± 11	32 ± 6	46 ± 6 ^a
Treatment C (NTG + analgesic dosage)	83 ± 17 ^a	60 ± 8 ^b	29 ± 5 ^b	42 ± 6 ^b

^a p < 0.05; ^b p < 0.001

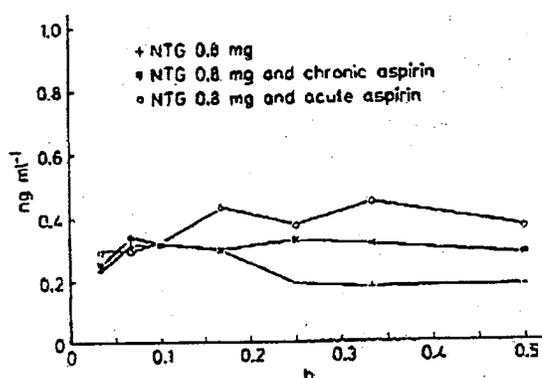


Fig. 1. Mean plasma level curves in the three treatment groups. A NTG 0.8 mg - - B NTG 0.8 mg and chronic aspirin - * C NTG 0.8 mg and acute aspirin - o

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Appendix IV
COVER SHEET AND OCPB FILING/REVIEW FORM

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
<i>NDA Number</i>	21-780	<i>Brand Name</i>	Nitroglycerin Lingual Spray
<i>OCPB Division (I, II, III)</i>	DPE I (HFD 860)	<i>Trade Name</i>	Nitro Mist
<i>Medical Division</i>	DCRDP (HFD 110)	<i>Drug Class</i>	Nitrate, organic
<i>OCPB Reviewer</i>	Lydia Velazquez, PharmD	<i>Indication(s)</i>	Acute relief of an attack or acute prophylaxis of angina pectoris due to CAD
<i>OCPB Team Leaders</i>	Patrick Marroum, Ph.D. Nhi Beasley, Pharm.D.	<i>Dosage Form</i>	Lingual Spray Solution
<i>Date of Submission</i>	June 18, 2004	<i>Dosing Regimen</i>	1 to 2 sprays PRN every 3 to 5 minutes up to 3 sprays within a 15-minute period
<i>Estimated Due Date of OCPB Review</i>	April 15, 2005	<i>Route of Administration</i>	Lingual
<i>PDUFA Due Date</i>	June 3, 2005	<i>Sponsor</i>	NovaDel Pharma, Inc.
<i>Division Due Date</i>	April 18, 2005	<i>Priority Classification</i>	Standard

CLIN. PHARM. AND BIOPHARM. INFORMATION

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	1		
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
body wt.				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	2		4 additional studies found in a literature search
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	COMMENTS		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	Lydia Velazquez	4-15-05		
Secondary reviewer Signature and Date	Patrick Marroum Nhi Beasley	4-15-05 4-15-05		

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/s/

Lydia Velazquez
4/15/05 04:36:22 PM
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Original NDA - CPB review

Patrick Marroum
4/15/05 06:04:55 PM
BIOPHARMACEUTICS

Nhi Beasley
4/15/05 06:08:57 PM
BIOPHARMACEUTICS

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