CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21134

MEDICAL REVIEW(S)

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NDA 21-134
NITROSTAT(Nitoglycerin) 0.6mg
MEDICAL REVIEW
CARDIO-RENAL DRUG PRODUCT DIVISION
HFD 110

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1.0 Introduction

The purpose of this New Drug Application (NDA 21-134) is to gain approval for a new compressed formulation of SL-GTN tablet (referred to as "new Nitrostat" formulation) that will be used for symptomatic relief of anginal symptoms due to coronary artery disease. Nitrostat is a sublingually administered nitroglycerin tablet used prophylactically and therapeutically for relief of anginal symptoms due to coronary artery disease.

1.01 Objectives

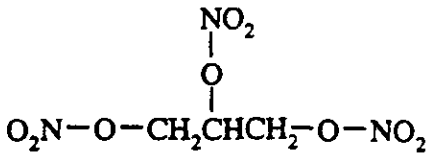
The stated objectives of this NDA are 1) to show that both Nitrostat formulations are superior to placebo and 2) that the new Nitrostat formulation is bioequivalent to the marketed tablet.

Mode of action

1.02 Nitroglycerin forms free radical nitric oxide (NO) which activates guanylate cyclase, resulting in an increase of guanosine 3'5' monophosphate (cyclic GMP) in smooth muscle and other tissues. These result in dephosphorylation of myosin light chains, which regulate the contractile state of smooth muscle, and subsequent vasodilatation.

1.03 The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle. Although venous effects predominate, nitroglycerin produces, in a dose-related manner, dilatation of both arterial and venous beds. Dilatation of postcapillary vessels, including large veins, promotes peripheral pooling of blood, decreases venous return to the heart, and reduces left ventricular end-diastolic pressure (preload). Nitroglycerin also produces arteriolar relaxation, thereby reducing peripheral vascular resistance and arterial pressure (afterload), and dilates large epicardial coronary arteries; however, the extent to which this latter effect contributes to the relief of exertional angina is unclear.

1.04 Nitroglycerin is an organic nitrate with a chemical name:1, 2, 3 propanetriol trinitrate and a chemical structure:



$C_3H_3N_3O_9$

Molecular weight: 227.09

Nitroglycerin was first introduced into clinical medicine in 1879[1] and Nitrostat has been marketed since 1938. Nitroglycerins have been the subject of several peer review publications, dealing with efficacy and safety in patients with angina[1-3]. The current treatment modalities for angina include β-blockers, calcium channel blockers, and nitrates. All are effective in correcting the imbalance between oxygen supply and demand by a different mechanism of action for each and the time to onset of pharmacological activity differs among different classes of antianginal drugs.

1.05 The current NDA describes the development of a compressed Nitrostat tablet with improved weight control, content uniformity, and physical stability. Previous investigations that supported reformulation of Nitrostat in the US had been conducted under IND and submitted to FDA The major components of the present NDA agreed upon by the sponsor, DCRDP, and DNDC1 include the following:

- Complete CMC information.
- Literature review of safety and efficacy of sublingual nitroglycerin.

- Clinical pharmacology study in normal subjects that will compare the kinetics of current and new formulation as well as compare both formulations using plethysmography.
- Clinical study of new formulation versus placebo in a crossover design in exercise tolerance using one high dose of 0.6mg. A sample size of 10 subjects is deemed adequate to show a difference from placebo (minutes-August 5, 1993; FDA-Parke-Davis meeting).
- The NDA however will not be required to generate data categorized by age and gender.
- Agreements were also reached on chemistry and biopharmaceutical questions particularly those posed by the sponsor (minutes of October 1, 1998).

1.07 There are several nitroglycerin formulations that are marketed globally for the treatment of angina pectoris. These include *Sublingual, Buccal, *Lingual spray, Long acting oral formulations, Dermal ointments, and Transdermal patches. (*Marketed in the US).The sublingual formulation has an established record of efficacy and safety in clinical practice and has been used as a positive control for testing efficacy of other nitroglycerins in clinical research for relief of angina. Therefore, the new reformulation in this NDA should demonstrate similar efficacy in the relief of angina, and be suitable for future development of generic formulations.

2.0 Bioavailability and Pharmacokinetics

Thirty-six healthy volunteers received 1 × 0.6 mg marketed Nitrostat, 2 × 0.3-mg new Nitrostat formulation, and 1 × 0.6 mg new Nitrostat formulation each on 1 occasion, 1 week apart, in an open-label, single-dose, randomized, 3-way crossover study (Study 782-16 See Figure 2, page 8). The pharmacokinetic parameter values for nitroglycerin, the ratios of values for comparisons, and 90% CIs are presented in Table 1 (page 4).

The mean Cmax value for 0.6 mg new Nitrostat formulation was 21% greater than that for 0.6 mg marketed Nitrostat. Similarly, the mean Cmax value for 2 × 0.3 mg new Nitrostat formulation was 34% greater than that for 0.6 mg marketed Nitrostat. This suggests that the rate of absorption of the new Nitrostat is greater than that of the marketed Nitrostat. However, based on less than 25% difference in mean area under plasma concentration-time curve from 0 to infinite time postdose [AUC(0-∞)] values, the extent of absorption after administration of the new Nitrostat formulation was similar, although somewhat greater than that for 0.6 mg marketed Nitrostat.

With respect to nitroglycerin, comparisons between each of the new Nitrostat formulations and marketed Nitrostat demonstrate a lack of bioequivalence because the 90% CIs for both Cmax and AUC were outside of the 80% to 125% range generally required to establish bioequivalence (See Table 1 in this review, page 4, and Table 1 in Dr Fadiran's review). The individual pharmacokinetic values obtained after administration of each formulation showed a great deal of overlap. The 90% confidence interval for Cmax and AUC in the comparison of 2 x0.3- and 0.6-mg new Nitrostat

formulations was just outside the bioequivalence range while that for AUC was within the range (95%-122%) (See Table 1 below page 4).
Using two metabolites 1,2-GDN and 1,3-GDN (Study 782-16), the new Nitrostat formulation (2 x 0.3mg, 1x 0.6mg) showed bioequivalence to the marketed Nitrostat tablet (1 x 0.6mg) (See Table 1 in Dr Fadiran's review).

The time to clinical effect for the 0.6mg new Nitrostat tablet formulation was delayed for about 30 seconds relative to the marketed Nitrostat tablet (See Figure 1, page 7). These findings may be relevant to the statistical reviewer's comment (See Dr Lawrence's review).

Table 1. Study 782-16: Pharmacokinetic Parameter Values for Nitroglycerin Obtained After Sublingual Doses of 1 × 0.6 mg Marketed Nitrostat, 2 × 0.3-mg New Nitrostat Formulation, and 1 × 0.6-mg New Nitrostat Formulation, the Ratios of the Values for Comparisons, and 90% Confidence Intervals

Parameter	Mean Values (n = 36)			90% Confidence Interval
	1 × 0.6 mg Marketed Nitrostat	1 × 0.6-mg New Nitrostat Formulation	Ratio	
Cmax (ng/mL)	1.42	1.72	121	103%-142%
tmax (min)	6.2	7.2	116	NA
AUC(0-tldc), min ng/mL	9.9	11.6	117	103%-133%
AUC(0-∞), min ng/mL	10.6	12.1	114	102%-130%
t½, min	3.2	2.6	119	NA
Parameter	1 × 0.6 mg Marketed Nitrostat	2 × 0.3-mg New Nitrostat Formulation	Ratio	90% Confidence Interval
Cmax (ng/mL)	1.42	1.90	134	113%-157%
tmax (min)	6.2	6.4	104	NA
AUC(0-tldc), min ng/mL	9.9	12.3	124	109%-141%
AUC(0-∞), min ng/mL	10.6	13.1	124	109%-140%
t½, min	3.2	2.8	87	NA
Parameter	1 × 0.6-mg New Nitrostat Formulation	2 × 0.3-mg New Nitrostat Formulation	Ratio	90% Confidence Interval
Cmax (ng/mL)	1.72	1.90	111	94%-130%
tmax (min)	7.2	6.4	89	NA
AUC(0-tldc), min ng/mL	11.6	12.3	106	94%-121%
AUC(0-∞), min ng/mL	12.1	13.1	108	95%-122%
t½, min	2.6	2.8	108	NA

Cmax = Maximum concentration; NA = Not applicable; tmax = Time to obtain maximum concentration; AUC = Area under the concentration-time curve; tldc = The last detectable concentration; t½ = Elimination half-live.

2.01 Summary of Bioequivalency

In summary, the rate and extent of drug absorption following administration of 2 x 0.3- and 0.6 mg new Nitrostat formulations and 0.6 mg marketed Nitrostat are similar. The Cmax and AUC values for the principal metabolites of nitroglycerin, 1,2-GDN, and 1,3-GDN, met generally accepted bioequivalency standards using FDA guidelines (See

Table 1 Biopharm Review). However, the extent of drug absorption from the new Nitrostat formulation is somewhat greater while the rate of absorption may be somewhat slower compared to the marketed Nitrostat tablet. This finding does not significantly affect the efficacy of the new formulation when compared to placebo.

3.0 Clincal Pharmacology

For this NDA submission, the vasodilatory component of nitroglycerin action was quantified by continuous digital plethysmography using a non-invasive, pharmacodynamic endpoint (finger BP) as surrogate for therapeutic effect.

3.1 Clinical Pharmacology Studies

Table 2 presents the demographics of subjects participating in the 2 open label studies (See Appendix, pp27-29). The subjects were predominantly white men (95%), and ages ranged from 18 to 34 years. In Study 782-13, all 20 subjects completed the study and in study 782-16, 36 out of 37 subjects completed the study (See pages 26-28).

3.2 Objectives

The study objectives were to evaluate the BP waveform as a pharmacodynamic endpoint, to describe the vasodilatation associated with sublingual marketed Nitrostat, and to determine inter- and intra-subject variability in pharmacodynamic response. Arterial BP waveforms as monitored with DPG were continuously recorded for 15 minutes before and 60 minutes after each marketed Nitrostat dose.

Statistical evaluation was performed on the data acquired for 5 minutes before and for 15 minutes after sublingual marketed Nitrostat administration, the postdose interval during which the parent compound would be expected to exert its maximal vasodilatory effect.

Study 782-16

This was an open label, single dose study, randomized, 3 way crossover study with 33 males and 3 females (Table 2) with a wash period of 7 days. Each subject was administered sublingually 1-3 of the treatment regimens after an overnight fast in a randomized fashion. Blood samples collected were analyzed and Blood pressure measured continuously for 15 minutes before and 30 minutes post-treatment using a digit plethysmography (DGP)(See Appendix page 27).The pharmacodynamic objective of Study 782-16 was to compare the effects of new Nitrostat formulation with those of marketed Nitrostat (0.3 and 0.6 mg) on the digital BP waveform during the period of expected maximal anti-anginal effect.

Study 782-13

This was an open-label, single dose, 3 period, repeated measures study to evaluate peripheral arterial vasodilatation associated with sublingual administration of marketed Nitrostat, using real time DSR, and to determine the inter- and intrasubject variability in the PD response in 20 healthy subjects. This study was not designed to compare the effects of the two formulations. The results of the comparative study was therefore based on study 782-16 above (Table 2 for demographics).

Table 2: Demographics of Subjects in open-label studies

Table 2. Clinical Pharmacology Studies				
Subject Characteristic	Study 782-13		Study 782-16	
	N = 20		N = 37	
Gender, N(%)				
Men	20	(100.0)	34	(91.9)
Women	0	(0.0)	3	(8.1)
Race, N(%)				
White	18	(90.0)	36	(97.3)
Black	1	(5.0)	0	(0.0)
Other	1	(5.0)	1	(2.7)
Age, year				
Mean	27.1		22.9	
Range	20.0-34.0		18.0-34.0	
Screening Weight, kg				
Mean	85.0		77.7	
Range	71.6-109.3		60.5-101.8	

3.2 Results of Pharmacodynamic Study (Variability Responses) 782-13

Comparison of systolic:diastolic ratio (SDR) response between doses and at 1 minute intervals (1-15) showed a 90%CI (non-log transformed) between 80-120% (Study 782-13) (Table 3) . After sublingual marketed Nitrostat administration, SDR increased to an overall mean maximal value (E_{100}) of 3.6 (Table 3). The within and among subject variability in E_{100}, E_{75}, E_{50}, and E_{25} were roughly the same as at baseline (predose), with coefficients of variation (CVs) about 10%. In contrast, the time to any specific level of effect demonstrated greater variability, both within (CV = 40.2%-43.6%) and among (CV = 23.6%-45.5%) subjects (Table 3). These findings suggest that the subjects achieved similar extents of vasodilatation from baseline to peak drug effect, but the times of occurrence at each level of effect varied considerably.

3.3 Results of Pharmacodynamic Effect Study 782-16

Comparisons of effects (SDR) between doses (90% CI) is presented in Table 4.
The times to effect for either of the new Nitrostat formulations as compared with marketed Nitrostat were consistently greater than those for marketed Nitrostat. For the 2×0.3-mg new Nitrostat formulation, the mean time (t_{100}) to E_{100} occurred 30 seconds later than it did for marketed Nitrostat. For the 1×0.6-mg new Nitrostat formulation, the mean t_{100} and t_{75} occurred 1 minute later than it did for marketed Nitrostat. These findings were supported by an examination of the mean SDR-time profiles (Figure 1). While the shapes of profiles appear identical for all 3 treatments, suggesting equivalence at all levels of effect, the postdose profiles for the compressed formulations were shifted to the right of the marketed Nitrostat profile by about 30 seconds.

e 3: **Study 782-13: Effect of Marketed Nitrostat Administered on 3 Occasions 1 Week Apart on Mean SDR Values, Mean Times to Effect 90% Confidence Intervals for Comparisons Between Doses 2 an 3 With Dose 1, and Variability of the Pharmacodynamic Responses Within and Among 20 Healthy Volunteers**

% of	Mean SDR			SDR-90% Confidence Intervals		Overall	Variability-CV (%)	
aximal Effect	Dose 1	Dose 2	Dose 3	Dose 1 vs Dose 2	Dose 3 vs Dose 1	Mean (SDR)	Within Subject	Among Subject
E0	2.5	2.4	2.4	92-100	91-100	2.4	7.8	8.2
E25	2.7	2.6	2.7	91-101	94-103	2.7	7.3	8.4
E50	3.1	2.9	3.0	89-99	92-102	3.0	9.1	9.0
E75	3.4	3.2	3.3	88-99	92-103	3.3	10.5	10.3
E100	3.7	3.5	3.6	87-99	92-104	3.6	11.8	11.7
Time to	Time to Maximal Effect			SDR-90% Confidence Intervals		Overall	Variability-CV (%)	
aximal Effect	(min)			Dose 1 vs Dose 2	Dose 3 vs Dose 1	Mean Time	Within Subject	Among Subject
(min)	Dose 1	Dose 2	Dose 3			(min)		
25	1.4	1.2	1.3	51-103	56-105	1.3	43.6	45.5
50	2.2	2.1	2.0	71-115	72-115	2.1	41.8	25.1
75	3.3	3.6	2.9	86-131	67-111	3.2	42.1	30.0
100	5.2	5.1	4.6	78-118	68-108	4.9	40.2	23.6

R = Systolic:Diastolic Ratio; TRT = Treatment; Doses 1, 2, and 3 = 1 × 0.6 mg Marketed Nitrostat; CV = Coefficient of variation.

Comparison of the SDR response between doses, using 90% CIs as used in pharmacokinetic bioequivalence evaluations, indicated that all levels of the pharmacodynamic effect (E_0 to E_{100}) easily met bioequivalence criteria.

Table 4: Comparisons of SDR between doses in Healthy Subjects

%Max Effect	Time to Effect	Mean SDR			90% CI	
		Dose1	Dose2	Dose3	Dose1vs 2	Dose 3 vs 1
0	-	2.5	2.4	2.4	92-100	91-100
25	1.3	2.7	2.6	2.7	91-100	94-103
50	2.1	3.1	2.9	3.0	89-99	93-102
75	3.2	3.4	3.2	3.3	88-99	92-103
100	4.9	3.7	3.5	3.6	87-99	92-104

4.0 Pharmacokinetic and Pharmacodynamic endpoints:

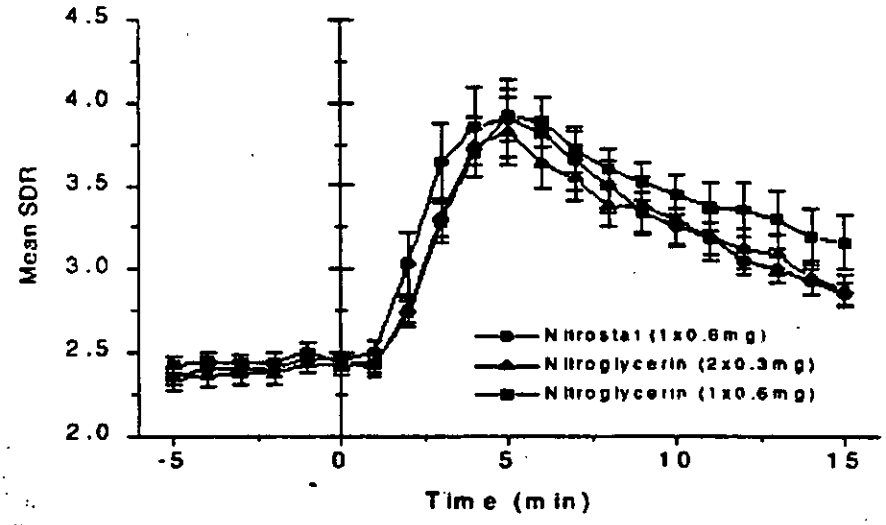
The population pharmacokinetic-pharmacodynamic analysis shows no significant difference in the pharmacodynamic effects (peripheral vasodilatation) in the 3 treatment groups (Protocol 782-16). This suggests that similar pharmacodynamic effects result from the administration of the new compressed Nitrostat formulation and the currently marketed Nitrostat tablet using digital plethysmography (See Biopharm review by Dr Mishina)[4-6].

5.0 Statistical evaluation for efficacy

The primary parameter for efficacy was exercise time to onset of moderate angina, and the secondary parameter was time to onset of myocardial ischemia. Exercise times to event (angina or myocardial ischemia) were compared between treatments using ANOVA. The model included center, treatment, sequence, period, and patient tested within sequence and center, as effects. Linear contrasts were used to compare new

Nitrostat formulation and marketed Nitrostat formulation to placebo[7-8]. Data from all randomized patients were used for all efficacy analyses. All tests were 2-sided and conducted at a 5% level of significance. In response to a letter from the FDA dated August 20, 1998, a test giving information on the similarity between the marketed and the new Nitrostat formulations was added to the statistical analyses.

Figure 1

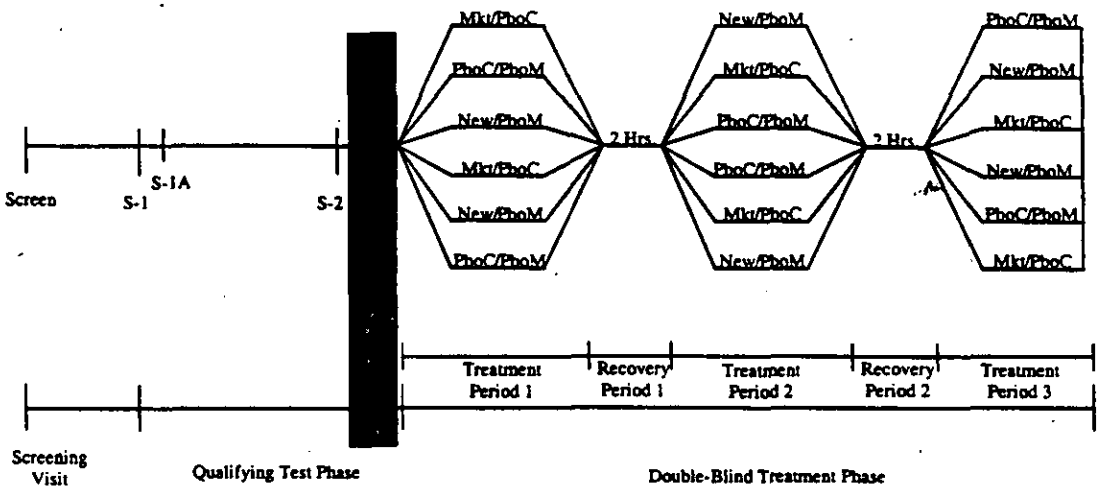


6.0 Clinical studies

Efficacy

There were two studies with identical design, 782-15 (single center study) and 782-17 (multicenter study). Each was a double-blind, 3 way, crossover study consisting of 3 phases: 1) screening; 2) qualifying; and 3) double-blind treatment phase (Figure 2).

Figure 2: Study Design (For ETT – Bruce Protocol in Appendix 2 page 30)



Mkt/PboC: Marketed Nitrostat tablet and compressed placebo tablet; 5-minute wait; Treadmill exercise test

New/PboM: New Nitrostat formulation tablet and molded placebo tablet; 5-minute wait; Treadmill exercise test

PboC/PboM: Compressed placebo tablet and molded placebo tablet; 5-minute wait; Treadmill exercise test

6.1 Demographics, characteristics and disposition of all subjects are in Tables 5-7.

Table 5: Demographics - Double blind Study - 782-17

TABLE 6. Baseline Patient Characteristics (All Randomized Patients)

Characteristic	Treatment Sequence Group						All Patients
	Mkt/New/Pbo N = 5	Pbo/Mkt/New N = 8	New/Pbo/Mkt N = 8	Mkt/Pbo/New N = 5	New/Mkt/Pbo N = 8	Pbo/New/Mkt N = 6	N=40
Sex N (%)							
Men	4 (80.0)	6 (75.0)	5 (62.5)	4 (80.0)	5 (62.5)	6 (100.0)	30 (75.0)
Women	1 (20.0)	2 (25.0)	3 (37.5)	1 (20.0)	3 (37.5)	0 (0.0)	10 (25.0)
Race, N (%)							
White	4 (80.0)	8 (100.0)	8 (100.0)	5 (100.0)	7 (87.5)	6 (100.0)	38 (95.0)
Hispanic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (2.5)
American Indian	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)
Age, Years							
Median	71	65	62	67	60.5	70	66
Range	63-78	47-77	52-71	39-74	51-78	64-80	39-80
Mean (SD)	70.2 (6.2)	63.9 (12.4)	62.0 (5.7)	62.8 (13.9)	63.6 (10.3)	70.8 (5.2)	65.1 (9.6)
BMI, kg/m^2	24.8	27.1	28.2	27.2	26.1	28.95	27.0
Median	21.5-31.0	23.8-37.9	22.5-46.2	23.88-32.7	23.2-34.6	24.2-31.7	21.5-46.2
Range	25.3 (3.6)	28.7 (5.8)	30.5 (7.7)	28.1 (3.7)	26.8 (3.5)	28.6 (3.0)	28.2 (4.9)
Mean (SD)							
Blood Pressure, mm Hg							
Systolic[a]							
Median	120	141	139	140	136	130	138
Range	102-156	110-156	100-170	110-142	114-184	118-172	100-184
Mean (SD)	125.6(22.2)	134 (17.1)	139 (22.0)	132.4(13.4)	141 (21.6)	136.7(18.7)	135.5(18.9)
Diastolic[b]							
Median	78	72	80	72	77	80	78
Range	60-80	60-92	50-88	60-92	70-90	70-100	50-100
Mean (SD)	73.6 (8.7)	75 (9.9)	76.3(11.8)	73.2(11.6)	78.0 (7.7)	81.3(11.4)	76.4 (9.9)
Heart Rate, bpm							
Median	64	67.5	66.5	54	59.5	72	60.5
Range	59-101	43-83	52-81	53-88	52-88	53-82	43-101
Mean (SD)	72.4(17.7)	65.5(14.3)	66.3 (9.7)	61.4 (14.99)	62.3(11.3)	70.0(12.5)	66.0(12.9)

[a] Sitting systolic blood pressure, predose

[b] Sitting diastolic blood pressure, predose

Table 6: Patient disposition - Double blind studies

Double-Blind Studies	Patients (n) randomized to 1/6 sequence groups	Completed Screening	Males Completed Study	Females Completed Study	Mean age	Race
782-15	35(100%)	35(100%)	33(94%)	2(6%)	62.2	W
782-17	55(100%)	55(100%)	30(75%)	10(25%)	66.0	W
Total	90	90	63	12	64	

Table 7-Patient disposition - Open label studies -782-13 and 782-16

Open label studies	Patients (n) Single dose, 3 period, SDR measures	Completed 3 doses, 1 week apart	Males	Females	Mean age (Range)	Race
782-13	20	20	20	0	27.1 (20-34)	18W,1B,1O
	Patients(n) Single-dose randomized 3 way crossover	Completed 3 doses, 1 week apart	Males	Females	Mean age (Range)	Race
782-16	37	36	34	3	22.9 (20-34)	36W,0B,1O
Total	57	56	54	3	25	

W=Whites, B=Blacks, O=Others.

6.2 Results

Primary efficacy

The mean times to onset of moderate angina in all randomized patients are summarized in Table 8 below. The vital signs and ST depression at ETT stage are in Tables 10 and 10b.

Table 8: Efficacy data in Double-Blind Study - 782-17

Time to onset (minutes)	Placebo(N=40)	New Nitrostat formulation(N=40)	Marketed Nitrostat (N=40)
Mean[bcd]	5.97	6.83	6.85
Standard error	0.21	0.25	0.26
Median	5.83	6.70	6.63
Minimum - Maximum	3.58-9.22	4.28-11.32	4.23-11.22

[b] p=0.00001; [c] p=0.00001; [d] p=0.8202

Both the new and marketed formulations resulted in an increase in mean time to onset of moderate angina of approximately 0.9 minutes compared to placebo. This is supported by a statistically significant difference between the mean times to onset of moderate angina between patients randomized to marketed Nitrostat compared to placebo - 6.85 versus 5.97 minutes (p=0.0001). Similarly, there is a significant difference between the mean

times to onset of angina between patients randomized to the new formulation compared to placebo 6.83 versus 5.97 minutes (p=0.0001). There is no significant difference between the marketed and the new formulation in time to onset of angina 6.85 versus 6.83 minutes (p=0.820) suggesting a clinical equivalence between the marketed and the new formulation. However, patients using the new formulation experienced moderate angina for an approximate period of 5% less compared to those using the old formulation. This temporal difference is so small that it should be deemed insignificant because of the small numbers of the subjects and for a tablet that will be used p.r.n (Tables 8 and 9).

Table 9: Estimated treatment differences for ETT-Study 782-17

Treatment Difference	Estimate	SE	p-value
Marketed versus New	0.039	0.171	0.820
Marketed versus Placebo	0.897	0.170	0.0001
New Formulation vs Placebo	0.858	0.170	0.0001

SE=Standard error

6.3 Secondary efficacy: The mean times to onset of myocardial ischemia

There is a statistically significant difference between the mean times to onset of myocardial ischemia (ST depression) between patients randomized to marketed Nitrostat compared to placebo (p=0.005). Similarly, there is a significant difference between the mean times to onset of myocardial ischemia (ST depression) between patients randomized to the new formulation compared to placebo (p=0.001). There is no significant difference between the marketed and the new formulation (p=0.775) suggesting that there is clinical equivalence between the marketed and new formulation (Table 10).

Table 10: Estimated treatment differences for ST depression of 1mm

Treatment Difference	Estimate	SE	p-value
Marketed versus New	-0.083	0.290	0.775
Marketed versus Placebo	0.833	0.283	0.005
New Formulation vs Placebo	0.917	0.269	0.001

SE=Standard error

Table 10b: Vital signs and ST segment depression - 782-17

Summary of Heart Rate, Blood Pressure and ST Segment Depression By Treatment Sequence Group and ETT Stage
All Randomized Patients
(Number (%) of Patients)

Protocol: 782-17

Before ETT - Sitting (Position)	40	128	73.9	[illegible]	[illegible]	74.3	40	128.9	74.6
Before ETT - Sitting (Position):	40	127.2	73.2	[illegible]	[illegible]	71.2	40	110.3	69.7
Before ETT - Standing	40	127.1	74.4	[illegible]	[illegible]	72.9	40	112.8	69.8
ETT Begins	39	128.7	75.9	[illegible]	[illegible]	72.4	40	113	69.9
Onset of Angina (P1)	38	153.2	79.1	[illegible]	[illegible]	77.1	22	153.6	80.1
ST Segment Depression of 1 mm	37	156.1	81.3	[illegible]	[illegible]	78.6	29	152.4	79.4
Termination of ETT (P2 or Pk Exercise)	40	163.7	[illegible]	[illegible]	[illegible]	77.2	40	159.9	78.3

7.0 Safety

Headache and dizziness were the two commonest treatment-associated adverse events in the two studies (Table 11). Vasodilatation and palpitations were also relatively frequent treatment-associated adverse events.

Adverse Events Study 782-13 PD (for tolerability and variability)
A total of 70 treatment-emergent adverse events (AEs) were reported by 17 of the 20 subjects who received marketed Nitrostat in ***Study 782-13***(Table 11). Fifty-eight of these AEs reported by 17 subjects were considered associated with treatment. Most AEs were mild in intensity. There were no deaths, serious AEs, or withdrawals due to AEs. During treatment with marketed Nitrostat, AEs occurred with the greatest frequency in the body as a whole and nervous system. The most frequently reported AEs and treatment-associated AEs were headache (39 reports in 17 subjects) and dizziness (7 reports in 5 subjects)(Table 11).

Adverse events -Study 782-16 – (Comparison of PD effects)
A total of 48 treatment-emergent AEs were reported by 20 of the 37 subjects who received either marketed or new or both marketed and new Nitrostat formulations in Study 782-16. All of these AEs were considered treatment associated. Most AEs were mild in intensity. There were no deaths or serious AEs. One subject was withdrawn due to syncope of moderate intensity. In the opinion of the investigator, the syncope was possibly related to the study medication. During treatment, AEs occurred with the greatest frequency in the body as a whole and cardiovascular system (Table 11). The most frequently reported AEs and treatment-associated AEs were headache (23 reports in 13 subjects) and vasodilatation (7 reports in 3 subjects) (Table 11).

Table 11: Clinical Pharmacology Studies: All and Associated [a] AEs by Body System [Number (%) of Exposures]

BODY SYSTEM/ Adverse Event	Study 782-13 Number of Exposures[b] (N = 60)				Study 782-16 Number of Exposures[c] (N = 109)			
	All		Associated		All		Associated	
BODY AS A WHOLE	39[d]	(65.0)	39	(65.0)	23	(21.1)	23	(21.1)
Headache	39	(65.0)	39	(65.0)	23	(21.1)	23	(21.1)
Pain	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
NERVOUS SYSTEM	8	(13.3)	7	(11.7)	5	(4.6)	5	(4.6)
Dizziness	7	(11.7)	7	(11.7)	5	(4.6)	5	(4.6)
Somnolence	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
RESPIRATORY SYSTEM	7[d]	(11.7)	3	(5.0)	0	(0.0)	0	(0.0)
Rhinitis	5	(8.3)	3	(5.0)	0	(0.0)	0	(0.0)
Pharyngitis	3	(5.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cough Increased	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
CARDIOVASCULAR SYSTEM	5	(8.3)	4	(6.7)	13[d]	(11.9)	13[d]	(11.9)
Bradycardia	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.9)
Hypotension	0	(0.0)	0	(0.0)	2	(1.8)	2	(1.8)
Syncope	0	(0.0)	0	(0.0)	2	(1.8)	2	(1.8)
Vasodilatation	3	(5.0)	2	(3.3)	7	(6.4)	7	(6.4)
Palpitation	2	(3.3)	2	(3.3)	3	(2.8)	3	(2.8)
DIGESTIVE SYSTEM	4	(6.7)	3	(5.0)	3[d]	(2.8)	3[d]	(2.8)
Nausea	2	(3.3)	2	(3.3)	3	(2.8)	3	(2.8)
Gastroenteritis	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Rectal Disorder	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.9)
Glossitis	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)
HEMIC AND LYMPHATIC SYSTEM	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphadenopathy	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES	1	(1.7)	0	(0.0)	1	(0.9)	1	(0.9)
Herpes Simplex	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Sweating	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.9)
SPECIAL SENSES	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)
Abnormal Vision	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)
Amblyopia	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)

[a] Considered by the investigator to be related to treatment.
[b] Patients received marketed Nitrostat.
[c] Patients received marketed or new or both marketed and new Nitrostat formulations.
[d] Total for a given body system may be less that the combined number of subjects reporting individual AEs because an individual may have more than one adverse event in a body system.

Serious Adverse Events

There were no serious AEs, deaths, or withdrawals due to AEs during the study.

Adverse events across treatment-sequence groups

Adverse events were summarized by treatment (at onset of AE), combining across treatment-sequence groups (Table 12). The percentage of patients experiencing AEs was the same for the new (15.0%) and marketed Nitrostat formulations (15.0%); fewer AEs were recorded during treatment with placebo (2.5%).

Table 12: Adverse events across treatment-sequence groups.

Table 12: Summary of All[a] AEs by Body System [Number (%) of Patients]						
BODY SYSTEM/ Adverse Event	Placebo Only N = 40		New Nitrostat Formulation N = 40		Marketed Nitrostat N = 40	
BODY AS A WHOLE	0	(0.0)	5	(12.5)	5	(12.5)
Headache	0	(0.0)	5	(12.5)	5	(12.5)
DIGESTIVE SYSTEM	1	(2.5)	0	(0.0)	0	(0.0)
Nausea	1	(2.5)	0	(0.0)	0	(0.0)
NERVOUS SYSTEM	0	(0.0)	1	(2.5)	1	(2.5)
Dizziness	0	(0.0)	1	(2.5)	1	(2.5)
TOTAL	1	(2.5)	6	(15.0)	6	(15.0)

[a] All AEs were considered possibly, probably, or definitely related to study drug, insufficient information, or no answer as indicated on the CRF.

Study 782-17

The most frequent AE was headache with both formulations (Table 12). Nine patients reported 10 headaches. Five (12.5%) of the headaches occurred during treatment with new Nitrostat formulation and 5 (12.5%) of the headaches occurred during treatment with marketed Nitrostat. One patient experienced 2 episodes of dizziness, 1 occurred during treatment with new Nitrostat formulation, and 1 occurred during treatment with marketed Nitrostat. One patient developed nausea during treatment with placebo.

Summary

The safety profiles between the new Nitrostat formulation and the currenmtly marketed formulation were similar. The new Nitrostat was well tolerated in all studies except for the commonest adverse events indicated in the label (See References, pages 31-32).

8.0 Discussion

The NDA seeks approval for a new compressed formulation of new Nitrostat tablet that can be marketed for the symptomatic relief of acute attack of angina due to coronary artery disease. The sponsor carried out two clinical studies (782-15 and 782-17) on this well known drug using only one dose 0.6mg (one tablet or 2x0.3mg tablets) of the new and marketed formulations. The results of the efficacy study show that the new formulation is superior to placebo using ETT, and time to ST depression as endpoints. These two endpoints are adequate to justify evaluation of symptomatic relief of acute anginal symptoms. Furthermore, there is mechanistic support that the new formulation showed superiority over placebo using using SDR measurements. Compared to the marketed tablets, the minor differences observed are not statistically significant and when these are evaluated in terms of clinical benefits and risks, they appear to be relatively insignificant.

This reviewer considers that the total number of ITT subjects (40) is small. There are only 3 (7.5%) females in the efficacy study out of a total of 40 that is not in accordance with the FDA guidelines. The statistical reviewer suggests that the new formulation cannot claim bioequivalence to the marketed tablet. However both formulations are superior to placebo.The following deficiencies of the efficacy study are noteworthy:

- Only one dose was used in the study – 0.6mg
- PK data are not available for some of the dose levels - 0.4mg
- Small numbers of females < 8%
- Minimal numbers of other races apart from whites <3%
- Tolerance to nitroglycerine was not evaluated in the new formulation.
- The proposed model in the protocol for statistical analysis did not include possible interactions between other covariates such as sex, age, and race (See statistical review). Other clinico-pharmacological variables that could be confounding factors in the statistical analyses of equivalence include documented differences in the AUC, Cmax, and tlag values between both formulations.
- Furthermore, the sponsors assumed that the mean ETT is a linear function of a subset of covariates, which may not be the case in these studies since time and treatment and time are not the only covariates (See statistical review by Dr Lawrence).

8.1 Conclusions

Regardless of the above deficiencies, the primary and secondary objectives of this NDA have been satisfied.

- Both the new and marketed formulations resulted in an increase in mean time to onset of moderate angina of approximately 0.9 minutes compared to placebo.
- There is a significant difference between the mean times to onset of myocardial ischemia (ST depression) between patients randomized to marketed Nitrostat compared to placebo (p=0.005).
- There is a significant difference between the mean times to onset of myocardial ischemia (ST depression) between patients randomized to the new formulation compared to placebo (p=0.001).

- There is no significant difference between the marketed and the new formulation (p=0.775) suggesting that there is clinical equivalence between the marketed and new formulation.
- The population pharmacokinetic-pharmacodynamic analysis shows no significant difference in the pharmacodynamic effects (peripheral vasodilatation) in the 3 treatment groups (Protocol 782-16). This suggests that similar pharmacodynamic effects result from the administration of the new compressed Nitrostat formulation and the currently marketed Nitrostat tablet using digital plethysmography.
- The rate and extent of drug absorption following administration of 0.3- and 0.6-mg new Nitrostat formulations and 0.6 mg marketed Nitrostat are similar.
- The Cmax and AUC values for the principal metabolites of nitroglycerin, 1,2-GDN, and 1,3-GDN, met generally accepted bioequivalency standards. However, the extent of drug absorption from the new Nitrostat formulation is somewhat greater while the rate of absorption may be somewhat slower compared to marketed Nitrostat.
- This study has demonstrated the following: 1) comparable level of clinical benefit at the 0.6mg dose level between the new and the marketed formulations.
- These are manifested by the following: a) The treatment effects on ST depression are similar between the marketed and the new tablets in patients with angina due to coronary artery disease, and b) The treatment effects on time to onset of angina/termination of ETT are also similar between the two formulations.
- The two commonest adverse events, headaches and dizziness, occurred with similar frequencies with both the new and the marketed formulations. These are acceptable as part of treatment benefits.

- The study deficiencies outlined above can be verified during the postmarketing period but should not impact the overall results of the NDA.

8.2 Recommendation

Equivalence in clinical benefits between the new compressed Nitrostat formulation and the marketed tablets has been demonstrated in this NDA. Superiority of the new compressed formulation over placebo has also been demonstrated. The data justify a recommendation that the new formulation is approvable and should be approved.

/S/

A.O.Williams, M.D.