# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75-091**

# BIOEQUIVALENCE

**OFFICE OF GENERIC DRUGS**
**DIVISION OF BIOEQUIVALENCE**

ANDA #75-091 SPONSOR: Mylan Pharmaceuticals Inc.
DRUG: Carbidopa and Levodopa
DOSAGE FORM: Extended Release Tablets STRENGTH: 50 mg/200 mg
REF. PRODUCT: Merck Sharp & Dohme's Sinemet® ER Tablets, 50 mg/200 mg.
TYPE OF STUDY: 3 studies (fasting, non-fasting and multiple dosing)
Study Site:

Phoenix International Life Sciences Inc.
2350 Cohen Street
Quebec, Canada

---

STUDY SUMMARY: The three studies under fasting, non-fasting and multiple dosing conditions are acceptable.

The firm's three bioequivalence studies demonstrated that the test product, Mylan's Carbidopa and Levodopa Extended Release Tablets, 50 mg/200 mg, lot #2C012B, and the reference listed product, Merck Sharp & Dohme's Sinemet® Extended Release Tablets, 50 mg/200 mg, Lot #A6735, are bioequivalent. Under fasting conditions, the 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% for Carbidopa and Levodopa. Under non-fasting conditions, the ratios of the test to the reference for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.2 for Carbidopa and Levodopa. Under multiple dosing conditions, the 90% confidence intervals for the log-transformed AUCt and Cmax were within the acceptable range of 80-125% for Carbidopa and Levodopa.

---

DISSOLUTION: The comparative dissolution testing data are acceptable.

---

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III
INITIAL: Z.W. DATE: 6/30/98

---

GROUP LEADER: Barbara Davit, Ph.D. BRANCH: III
INITIAL: B.M.D. DATE: 6/30/98

---

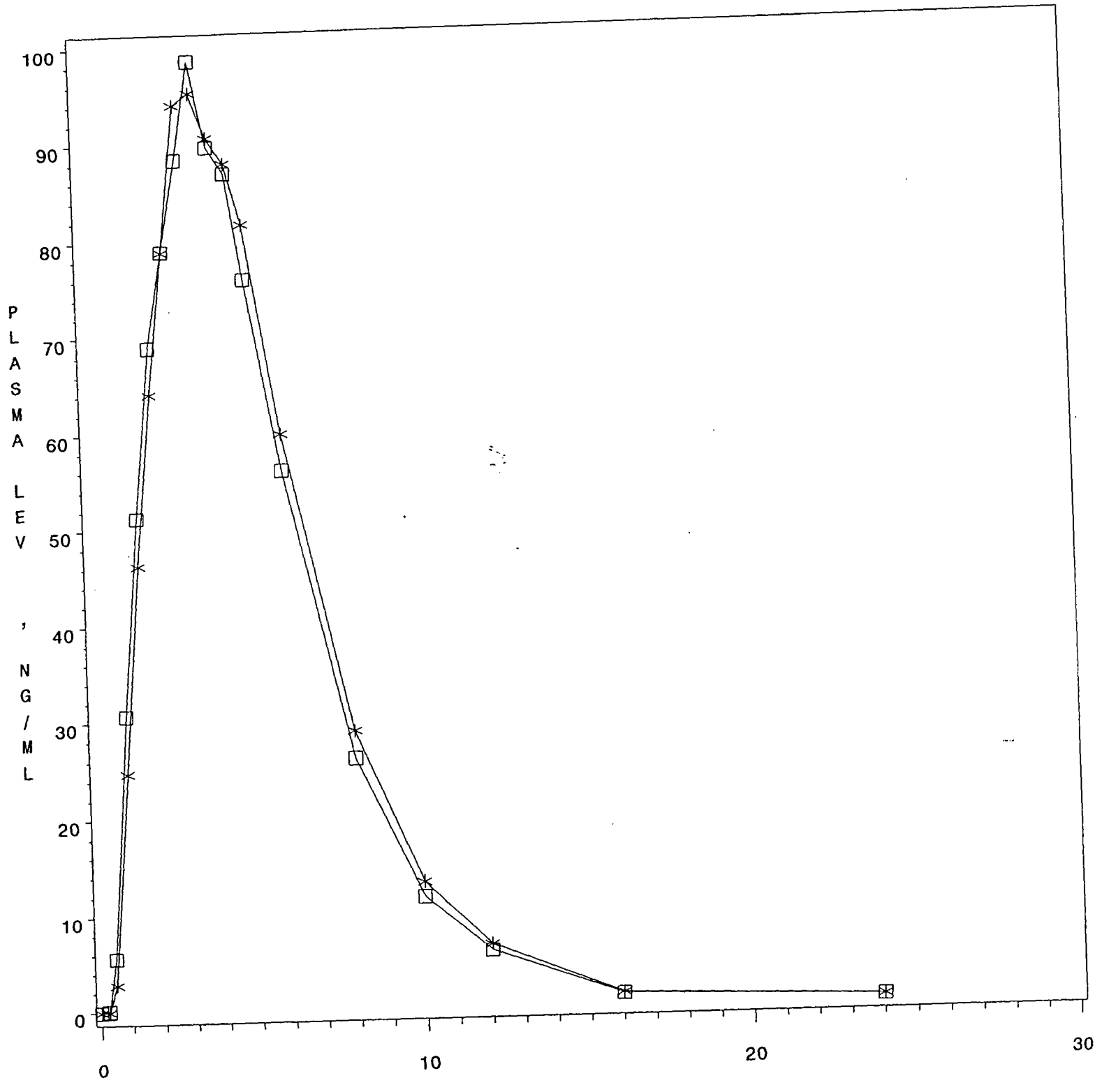
ACTING DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE
INITIAL: DPC DATE: 7/1/98

---

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: _____ DATE: _____

# FIG P#1. PLASMA CARBIDOPA LEVELS

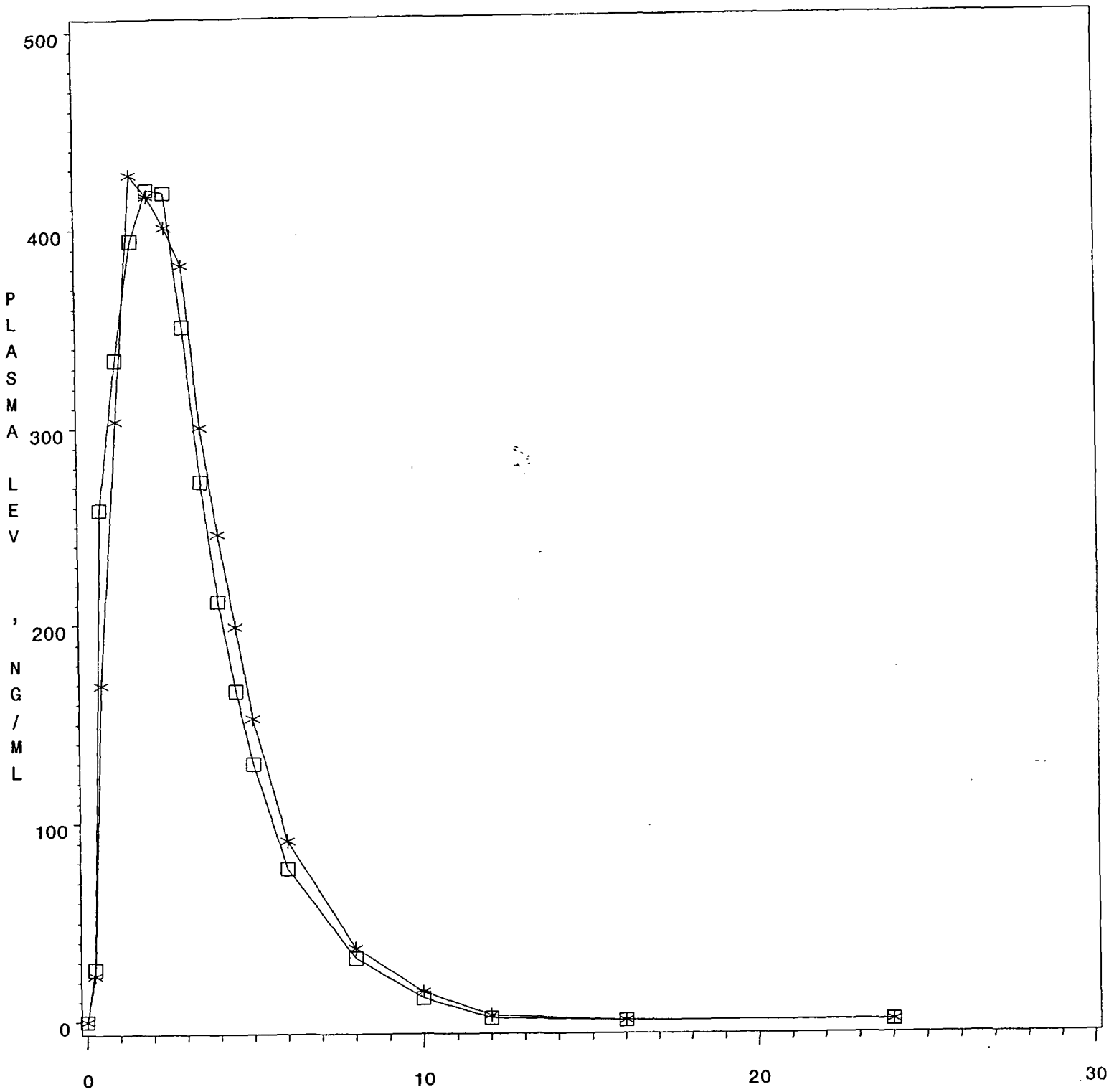
CARBIDOPA AND CARBIDOPA ER TABLETS, 25 MG/100 MG, ANDA #75-091
UNDER FASTING CONDITIONS
DOSE=1 X 25 MG/100 MG




1=TEST(MYLAND) 2=REF(DUPONT)

# FIG P#2. PLASMA LEVODOPA LEVELS

CARBIDOPA AND CARBIDOPA ER TABLETS, 25 MG/100 MG, ANDA #75-091
UNDER FASTING CONDITIONS
DOSE=1 X 25 MG/100 MG




1=TEST(MYLAND) 2=REF(DUPONT)

Attachment #1

# COMPARATIVE QUANTITATIVE COMPOSITIONS
# CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS, 25MG/100MG AND 50MG/200MG

| | 25MG/100MG | | 50MG/200MG | |
|---|---|---|---|---|
| | MG PER TABLET | % | MG PER TABLET | % |
| Carbidopa, USP | 27.0* | 18.0% | 54.0 | 18.0% |
| Levodopa, USP | | | | |
| *Granulating Solution Consists of:*[1] | | | | |

[G:\PROJECT\ANDA\CARBIDOPA-LEVODOPA-ER-TABS-25_100MG\SECTIONS-01THRU07.WPD

Attachment #2

# DISSOLUTION PROFILE

PRODUCT: Carbidopa/Levodopa Extended-release Tablets
LOT NO.: 2D002K
DOSAGE: 25 mg/100 mg

PROCEDURE: FP-CDLDER-DS-M DATE OF ASSAY: 12/05/97

CONDITION: **Dissolution Medium:** 0.1 N Hydrochloric Acid; 900 mL @ 37.0°C ± 0.5°C
**Limits:** 30 minutes:
60 minutes:
150 minutes:
240 minutes:
**Apparatus:** 2 (paddles) @ 50 rpm
**Sample Times:** 30, 60, 150, 240 minutes

**(Carbidopa Portion)**

| | Time 30 min | Time 60 min | Time 150 min | Time 240 min |
|---|---|---|---|---|
| 1. | 26% | 47% | 84% | 101% |
| 2. | 16% | 38% | 74% | 96% |
| 3. | 20% | 39% | 74% | 95% |
| 4. | 20% | 39% | 73% | 96% |
| 5. | 29% | 51% | 93% | 97% |
| 6. | 22% | 46% | 84% | 99% |
| 7. | 28% | 55% | 96% | 100% |
| 8. | 29% | 50% | 91% | 99% |
| 9. | 28% | 54% | 94% | 101% |
| 10. | 28% | 44% | 85% | 101% |
| 11. | 25% | 42% | 80% | 97% |
| 12. | 27% | 50% | 90% | 100% |
| MEAN | 25% | 46% | 85% | 99% |
| RANGE | | | | |
| SD | 4.3 | 6.1 | 8.1 | 2.2 |
| RSD | 17.2% | 13.2% | 9.5% | 2.3% |

PREPARED BY J. Hartman DATE 12-21-98
APPROVED BY [signature] DATE 12-21-98

Attachment #3

# DISSOLUTION PROFILE

PRODUCT: *Carbidopa/Levodopa Extended-release Tablets*
LOT NO.: 2D002K
DOSAGE: 25 mg/100 mg

PROCEDURE: FP-CDLDER-DS-M DATE OF ASSAY: 12/05/97

CONDITION: **Dissolution Medium:** 0.1 N Hydrochloric Acid; 900 mL @ 37.0°C ± 0.5°C
**Limits:** 30 minutes:
60 minutes:
150 minutes:
240 minutes
**Apparatus:** 2 (paddles) @ 50 rpm
**Sample Times:** 30, 60, 150, 240 minutes

**(Levodopa Portion)**

| | Time 30 min | Time 60 min | Time 150 min | Time 240 min |
|---|---|---|---|---|
| 1. | 27% | 48% | 85% | 103% |
| 2. | 21% | 39% | 76% | 98% |
| 3. | 20% | 37% | 80% | 96% |
| 4. | 20% | 38% | 75% | 103% |
| 5. | 28% | 51% | 94% | 101% |
| 6. | 25% | 45% | 89% | 101% |
| 7. | 30% | 60% | 98% | 103% |
| 8. | 27% | 51% | 97% | 104% |
| 9. | 27% | 55% | 97% | 103% |
| 10. | 29% | 51% | 86% | 103% |
| 11. | 24% | 42% | 81% | 101% |
| 12. | 27% | 55% | 93% | 102% |
| MEAN | 25% | 48% | 88% | 101% |
| RANGE | | | | |
| SD | 3.5 | 7.5 | 8.2 | 2.5 |
| RSD | 13.9% | 15.8% | 9.4% | 2.4% |

PREPARED BY Goldman DATE 12-21-98
APPROVED BY [signature] DATE 12/21/98

Attachment #4

## DISSOLUTION PROFILE

**PRODUCT:** Sinemet® CR
**LOT NO.:** E6402
**DOSAGE:** 25 mg/100 mg

**PROCEDURE:** FP-CDLDER-DS-M **DATE OF ASSAY:** 12/05/97

**CONDITION:**
**Dissolution Medium:** 0.1 N Hydrochloric Acid; 900 mL @ 37.0°C ± 0.5°C
**Limits:**
30 minutes:
60 minutes:
150 minutes:
240 minutes
**Apparatus:** 2 (paddles) @ 50 rpm
**Sample Times:** 30, 60, 150, 240 minutes

**(Carbidopa Portion)**

| | Time 30 min | Time 60 min | Time 150 min | Time 240 min |
|---|---|---|---|---|
| 1. | 54% | 84% | 104% | 105% |
| 2. | 36% | 55% | 93% | 99% |
| 3. | 45% | 74% | 97% | 98% |
| 4. | 46% | 75% | 98% | 100% |
| 5. | 44% | 72% | 95% | 97% |
| 6. | 44% | 72% | 102% | 102% |
| 7. | 39% | 67% | 99% | 99% |
| 8. | 47% | 73% | 98% | 100% |
| 9. | 37% | 63% | 93% | 94% |
| 10. | 39% | 61% | 94% | 97% |
| 11. | 39% | 64% | 97% | 98% |
| 12. | 37% | 62% | 95% | 98% |
| MEAN | 42% | 69% | 97% | 99% |
| RANGE | | | | |
| SD | 5.3 | 7.9 | 3.4 | 2.7 |
| RSD | 12.6% | 11.5% | 3.5% | 2.7% |

PREPARED BY Goldsman DATE 12-21-98
APPROVED BY [signature] DATE 12-21-98

G:\RDLAB\BLEND\Sinemet E6402

Attachment #5

# DISSOLUTION PROFILE

**PRODUCT:** Sinemet® CR
**LOT NO.:** E6402
**DOSAGE:** 25 mg/100 mg

**PROCEDURE:** FP-CDLDER-DS-M **DATE OF ASSAY:** 12/05/97

**CONDITION:** **Dissolution Medium:** 0.1 N Hydrochloric Acid; 900 mL @ 37.0°C ± 0.5°C
**Limits:** 30 minutes:
60 minutes:
150 minutes:
240 minutes:
**Apparatus:** 2 (paddles) @ 50 rpm
**Sample Times:** 30, 60, 150, 240 minutes

**(Levodopa Portion)**

| | Time 30 min | Time 60 min | Time 150 min | Time 240 min |
|---|---|---|---|---|
| 1. | 57% | 85% | 106% | 110% |
| 2. | 35% | 58% | 95% | 102% |
| 3. | 50% | 75% | 100% | 101% |
| 4. | 47% | 76% | 100% | 102% |
| 5. | 48% | 73% | 98% | 101% |
| 6. | 45% | 73% | 103% | 105% |
| 7. | 41% | 66% | 100% | 102% |
| 8. | 47% | 75% | 103% | 104% |
| 9. | 39% | 63% | 97% | 99% |
| 10. | 40% | 66% | 99% | 101% |
| 11. | 39% | 66% | 100% | 101% |
| 12. | 37% | 63% | 98% | 101% |
| MEAN | 44% | 70% | 100% | 103% |
| RANGE | | | | |
| SD | 6.4 | 7.4 | 2.9 | 2.8 |
| RSD | 14.6% | 10.6% | 2.9% | 2.8% |

PREPARED BY Baldeman DATE 12-21-98
APPROVED BY [signature] DATE 12-21-98

G:\RDLAB\BLENDSinemet E6402

**Carbidopa & Levodopa ER Tablets**
25 mg/100 mg
ANDA #75-091
Reviewer: Z.Z. Wahba
File #75091sd2.D98

**Mylan Pharmaceuticals Inc.**
Morgantown, WV
Submission Date:
December 31, 1998

# REVIEW OF AN IN VIVO BIOEQUIVALENCE STUDY, AND IN VITRO DISSOLUTION TESTING DATA

## I. OBJECTIVE:

To review:

1. Mylan's in vivo bioequivalence study (single-dose under fasting conditions) comparing its test product Carbidopa and Levodopa Extended Release Tablets, 25 mg/100 mg to the reference listed product, Merck Sharp & Dohme's Sinemet® Extended Release Tablets, 25 mg/100 mg.

2. Dissolution profiles comparing Mylan's Carbidopa and Levodopa Extended Release Tablets, 25 mg/100 mg to the reference listed drug Merck Sharp & Dohme's Sinemet® Extended Release Tablets, 25 mg/100 mg.

## II. BACKGROUND:

Levodopa is the levorotatory isomer of dihydroxyphenylalanine and the metabolic precursor of dopamine. The drug is used in the treatment of Parkinsonian syndrome. Levodopa is commercially available alone or in combination with carbidopa. Carbidopa is a decarboxylase inhibitor which inhibits decarboxylation of levodopa to dopamine. Concurrent administration of carbidopa inhibits the peripheral decarboxylation of levodopa without affecting the metabolism of the drug within the CNS. Thus, more levodopa is available for transport to the brain.

Levodopa is rapidly and well absorbed from the GI tract. About 40-70% of carbidopa dose is absorbed following oral administration. Although levodopa does not appear to enhance the absorption of carbidopa, carbidopa may enhance the absorption of levodopa by suppressing the metabolism of levodopa in the GI tract. Plasma levodopa concentrations are increased when carbidopa and levodopa are administered concomitantly, principally because of inhibition by carbidopa of the peripheral metabolism of levodopa.
Levodopa is widely distributed into most body tissues and the total volume of distribution is about 65% of body weight. Probably less than 1% of absorbed levodopa penetrates the CNS and only a small amount enters the brain. Therefore, large doses of levodopa are required for adequate therapeutic effect and these may often be accompanied by nausea and other adverse reactions. Carbidopa is

also widely distributed into most body tissues; however, it does not cross the blood-brain barrier.

The plasma half-life of levodopa is approximately 1 hour. The plasma half-life of carbidopa is 1-2 hours. When carbidopa and levodopa are administered concurrently, the plasma half-life of levodopa is increased to about 2 hours. Most of the absorbed levodopa is decarboxylated to dopamine and small amounts of levodopa are metabolized to norepinephrine, epinephrine, 3-methoxytyramine, and 3-O-methyldopa. Dopamine is further metabolized to 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) and excreted in urine. Carbidopa is not extensively metabolized. When carbidopa and levodopa are administered concurrently, 60% of unchanged levodopa excreted in urine.

Levodopa is commercially available alone in three strengths: 100 mg, 250 mg and 500 mg tablets. Carbidopa and levodopa combination tablets are commercially available in three strengths: 10 mg/100 mg, 25 mg/100 mg, 25 mg/250 mg and as sustained-release 50 mg/200 mg SinemetR CR (Merck Sharp & Dohme).

## III. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER FASTING CONDITIONS
(Mylan Protocol #CBLV-9720, Phoenix Protocol #972913)

### A. Study Information:

Sponsor: Mylan Pharmaceuticals, Inc.
Clinical Facility: Phoenix International Life Sciences, Inc.
Principal Investigator: Samuel Serfaty, M.D.
Scientific Director:
Analytical Facility:

### B. Treatment Plan:

| | |
|---|---|
| Study design | Single dose, randomized, two-way crossover study under fasting conditions. |
| Treatment | A=Test prod. (Mylan's Carbidopa and Levodopa Extended Release Tablet, 25/100 mg)<br>B=Ref. Prod. (Merck Sharp & Dohme's Sinemet® Extended Release Tablet, 25/100 mg) |
| Dose administered | each dosing treatment 1X 25/100 mg ER tablet |
| Lot\Batch # | Test = Lot #2D002K<br>Reference = Lot #E6402 |

| | |
|---|---|
| Lot\Batch size | Test = units |
| Content Uniformity | Test Product<br>Carbidopa = 96.8%, Levodopa = 99.0%<br><br>Reference Product<br>Carbidopa = 99.5%, Levodopa = 99.8% |
| Potency | Test Product<br>Carbidopa = 97.5%, Levodopa = 99.4%<br><br>Reference Product<br>Carbidopa = 97.3%, Levodopa = 98.5% |
| Test manufacturing date (or expiration for Ref.) | Test = 11/19/97<br>Ref. = 07/99 |
| No. of subjects | Enrolled=47 (males), completed=44 (males). 44 subjects were used for statistical analysis (subjects #1-19, 21-23, 25-33 and 35-47). |
| Drop-outs | Subjects #20, 24 and 34 elected to withdraw from the study prior to Period-2 dosing for personal reasons. |
| Food & Fluid Intake | Subjects fasted overnight for at least 10 hours before dosing and 5 hours after dosing. The drug products were administered with 240 mL of water at room temperature. Water was not permitted for 1 hr before and 1 hr after dosing. Standard meals were provided at appropriate times thereafter. |
| Clinical study dates | Period I= 01/10/98; Period II= 01/17/98 |
| Wash out period | 7 days |
| Blood sampling | pre-dose (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16 and 24 hours. |

C. **Averse Events**:
(pages 1449, 1454 and 1626-1633, Clinical Report section, volume C3.4). No serious medical events were reported during the study.

D. **Assay Methodology**: **(NOT TO BE RELEASED UNDER FOI)**
(See volume C3.2, the Analytical Report Section)

| Analytical method | |
|---|---|
| Analyte | Plasma carbidopa<br>Plasma Levodopa |
| Sensitivity (LOQ) | Carbidopa = 4.0 ng/mL<br>Levodopa = 10.0 ng/mL |
| Quality control (QC) samples | Carbidopa: 10.0, 600.19, 800.26 ng/mL<br>Levodopa: 25.10, 803.20, 1606.40 ng/mL |
| QC samples - validation (between days) | Carbidopa:<br>Precision (CV%)= 7.1 to 10.4%<br>Accuracy (%)= 93.8 to 99.0%<br><br>Levodopa:<br>Precision (CV%)= 4.7 to 7.5%<br>Accuracy (%)= 97.1 to 100.3% |
| Linearty | Carbidopa: 4.0-1003 ng/mL<br>Levodopa: 10.0-2006 ng/mL |
| Calibration curve validation | Carbidopa:<br>Precision (CV%)= 5.8-9.0%<br>Accuracy (%)= 94.0 to 107.7%<br><br>Levodopa:<br>Precision (CV%)= 3.3-9.9%<br>Accuracy (%)= 97.6 to 103.3% |
| Recovery (extracted samples) | Carbidopa:<br>% recovery range of 32.5 to 33.5% (over QC concentrations of 19.67 to 157.35 ng/mL)<br><br>Levodopa:<br>% recovery range of 76.4 to 79.4% (over QC concentrations of 74.04 to 1579.61 ng/mL) |
| Stability | * Long term: both carbidopa and levodopa were stable |

| | |
|---|---|
| | for 123 days @ -80°C<br>* Short term: Stable @ room temp. for up to 3.5 hours<br>* Freeze/thaw Stability: for 3 cycles |

## E. IN VIVO BE STUDY & STATISTICAL ANALYSIS:

The plasma concentrations and pharmacokinetic parameters of carbidopa and levodopa were analyzed using SAS-GLM procedure for analysis of variance. Plasma carbidopa and levodopa levels, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

**FOR CARBIDOPA**

**Table #1**

**Mean Plasma Concentrations of Carbidopa (ng/mL) in 44 Subjects Following a Single Oral Dose of 1x(25mg/100mg Carbidopa/Levodopa ER tablet), Under Fasting Conditions**

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| TIME HR | | | | | |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | . |
| 0.25 | 0.00 | 0.00 | 0.10 | 0.68 | 0.00 |
| 0.5 | 2.84 | 3.79 | 5.66 | 5.68 | 0.50 |
| 1 | 24.77 | 14.28 | 30.70 | 17.31 | 0.81 |
| 1.5 | 46.26 | 19.00 | 51.28 | 21.59 | 0.90 |
| 2 | 64.12 | 23.14 | 68.93 | 30.66 | 0.93 |
| 2.5 | 78.85 | 34.60 | 78.97 | 29.05 | 1.00 |
| 3 | 94.03 | 37.70 | 88.37 | 31.74 | 1.06 |
| 3.5 | 95.27 | 43.40 | 98.54 | 38.56 | 0.97 |
| 4 | 90.56 | 43.89 | 89.63 | 33.63 | 1.01 |
| 4.5 | 87.88 | 44.06 | 86.86 | 42.05 | 1.01 |
| 5 | 81.58 | 42.25 | 75.88 | 36.55 | 1.08 |
| 6 | 59.74 | 30.12 | 55.90 | 32.91 | 1.07 |
| 8 | 28.64 | 16.23 | 25.92 | 14.84 | 1.11 |
| 10 | 13.03 | 8.42 | 11.52 | 7.32 | 1.13 |
| 12 | 6.33 | 4.94 | 5.70 | 4.38 | 1.11 |
| 16 | 0.92 | 2.39 | 0.82 | 1.97 | 1.11 |
| 24 | 0.11 | 0.71 | 0.10 | 0.65 | 1.09 |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

## Table #2
## Mean Pharmacokinetic Parameters (Arithmetic) for Carbidopa in 44 Subjects Following a Single Oral Dose of 1x(25mg/100mg Carbidopa/Levodopa ER tablet), Under Fasting Conditions

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI | 557.77 | 199.85 | 538.71 | 190.25 | 1.04 |
| AUCT | 537.75 | 198.26 | 524.73 | 189.15 | 1.02 |
| CMAX | 115.20 | 46.95 | 116.38 | 42.56 | 0.99 |
| KE | 0.34 | 0.09 | 0.34 | 0.09 | 1.00 |
| *LAUCI | 523.64 | 0.37 | 508.26 | 0.35 | 1.03 |
| *LAUCT | 502.63 | 0.38 | 493.32 | 0.36 | 1.02 |
| *LCMAX | 106.08 | 0.42 | 109.00 | 0.38 | 0.97 |
| THALF | 2.20 | 0.74 | 2.17 | 0.56 | 1.01 |
| TMAX | 3.57 | 0.99 | 3.70 | 0.96 | 0.96 |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
* The values represent the geometric mean (antilog of the means of the logs).

## Table #3
## LSMeans And The 90% Confidence Intervals For Carbidopa (Under Fasting Conditions)

| | LSM1 | LSM2 | RLSM12 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| LAUCI | 531.49 | 512.71 | 1.04 | 95.10 | 113.00 |
| LAUCT | 501.80 | 495.88 | 1.01 | 92.86 | 110.27 |
| LCMAX | 105.56 | 109.48 | 0.96 | 87.32 | 106.47 |

UNIT: AUC=NG HR/ML CMAX=NG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

Comment on the fasting study (Carbidopa):
The mean plasma carbidopa levels for the test and reference products were comparable to each other as shown in Table #1 and Figure #1. The 90% confidence intervals for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3). The T/R mean ratios (RLSM12) for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25% (Table #3).

**FOR LEVODOPA:**

Table #4

Mean Plasma Concentrations of Levodopa (ng/mL) in 44 Subjects Following a Single Oral Dose of 1x(25mg/100mg Carbidopa/Levodopa ER tablet), Under Fasting Conditions

| TIME HR | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | . |
| 0.25 | 23.39 | 45.51 | 26.54 | 39.79 | 0.88 |
| 0.5 | 169.60 | 121.54 | 258.90 | 159.70 | 0.66 |
| 1 | 303.84 | 148.62 | 334.57 | 155.60 | 0.91 |
| 1.5 | 427.48 | 140.39 | 394.51 | 139.46 | 1.08 |
| 2 | 416.78 | 117.90 | 419.89 | 169.84 | 0.99 |
| 2.5 | 401.06 | 136.89 | 418.33 | 145.31 | 0.96 |
| 3 | 381.75 | 116.82 | 350.54 | 131.42 | 1.09 |
| 3.5 | 300.35 | 93.56 | 272.54 | 83.41 | 1.10 |
| 4 | 245.99 | 87.42 | 211.75 | 74.76 | 1.16 |
| 4.5 | 198.90 | 93.63 | 166.57 | 58.79 | 1.19 |
| 5 | 152.57 | 55.39 | 129.63 | 44.61 | 1.18 |
| 6 | 90.75 | 34.39 | 76.82 | 29.37 | 1.18 |
| 8 | 36.85 | 17.75 | 31.88 | 13.29 | 1.16 |
| 10 | 14.67 | 10.61 | 11.42 | 10.02 | 1.28 |
| 12 | 2.82 | 5.85 | 1.41 | 4.54 | 2.00 |
| 16 | 0.00 | 0.00 | 0.00 | 0.00 | . |
| 24 | 0.00 | 0.00 | 0.00 | 0.00 | . |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table #5

Mean Pharmacokinetic Parameters (Arithmetic) for Levodopa in 44 Subjects Following a Single Oral Dose of 1x(25mg/100mg Carbidopa/Levodopa ER tablet), Under Fasting Conditions

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI | 1797.23 | 327.14 | 1712.68 | 320.40 | 1.05 |
| AUCT | 1749.56 | 326.22 | 1673.81 | 315.29 | 1.05 |
| CMAX | 545.40 | 113.16 | 570.71 | 152.96 | 0.96 |
| KE | 0.46 | 0.07 | 0.45 | 0.07 | 1.02 |
| *LAUCI | 1766.72 | 0.19 | 1684.23 | 0.18 | 1.05 |
| *LAUCT | 1718.26 | 0.20 | 1645.71 | 0.19 | 1.04 |
| *LCMAX | 533.92 | 0.21 | 552.24 | 0.26 | 0.97 |
| THALF | 1.54 | 0.23 | 1.58 | 0.26 | 0.98 |
| TMAX | 1.91 | 0.82 | 1.75 | 0.72 | 1.09 |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
* The values represent the geometric mean (antilog of the means of the logs).

**Table #6**
**LSMeans And The 90% Confidence Intervals**
**For Levodopa (Under Fasting Conditions)**

| | LSM1 | LSM2 | RLSM12 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| LAUCI | 1760.91 | 1691.38 | 1.04 | 100.66 | 107.68 |
| LAUCT | 1718.76 | 1646.47 | 1.04 | 100.82 | 108.09 |
| LCMAX | 533.60 | 552.02 | 0.97 | 91.02 | 102.65 |

UNIT: AUC=NG HR/ML CMAX=NG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

Comment on the fasting study (Levodopa):

The mean plasma levodopa levels for the test and reference products were comparable to each other as shown in Table #4 and Figure #2. The 90% confidence intervals for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #6). The T/R mean ratios (RLSM12) for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25% (Table #5).

**IV. FORMULATION COMPARISON:** (vol. C3.5, p #2261)

Mylan's formulation for its test product, Carbidopa/Levodopa ER Tablets, 25 mg/100 mg, is included in this report (Attachment #1).

**V. IN VITRO DISSOLUTION TESTING:** (vol. C3.5, pp #2251-715)

The dissolution testing for the test and reference products are summarized below:

Method: USP 23 apparatus II (paddle) at 50 rpm
Medium: 900 mL of 0.1N HCl
Number of Tablets: 12

Test products: Mylan's Carbidopa/Levodopa ER Tablets, 25 mg/100 mg, lot #2D002K

Reference products: Sinemet® CR Tablets, 25 mg/100 mg, lot#E6402

The firm's specification to control the dissolution rate are as follows:

| Time (minutes) | %Released |
|---|---|
| 30 | |

| | |
|---|---|
| 60 | NLT |
| 150 | NLT |
| 240 | NLT |

Results: Copies of the dissolution data statements are included in this report (Attachments #2-5).

**VI. RECOMMENDATIONS:**

1. The single-dose fasting bioequivalence study #CBLV-9720, conducted by Mylan Pharmaceuticals Inc., on its Carbidopa and Levodopa, 25 mg/100 mg extended release (ER) Tablet, lot #2D002K, comparing it to Sinemet® CR 25 mg/100 mg tablet, manufactured by Merck Sharp & Dohme, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Maylan's Carbidopa and Levodopa, 25 mg/100 mg extended release (ER) Tablet is bioequivalent to Sinemet® CR 25 mg/100 mg tablet's Sinemet® CR 25 mg/100 mg tablet.

2. The dissolution testing conducted by Mylan Pharmaceuticals Inc., on its Carbidopa and Levodopa, 25 mg/100 mg extended release (ER) Tablet, lot #2D002K is acceptable. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data the following tentative specifications are recommended for Carbidopa and Levodopa:

    0.5 hour
    1.0 hour
    2.5 hours
    4 Hours

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT BNB 2/24/99
FT INITIALLED BDAVIT (Barbara Ann Davit) 2/24/99

Concur: Dale P. Conner Date: 2/24/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

2./

**Carbidopa & Levodopa ER Tablets**
50 mg/200 mg
ANDA **#75-091**
Reviewer: Z.Z. Wahba
File #75091a.j98

**Mylan Pharmaceuticals Inc.**
Morgantown, WV
Submission Date:
January 23, 1998
June 19, 1998

## REVIEW OF AN AMENDMENT

### BACKGROUND

1. The firm has previously submitted three in vivo bioequivalence studies (single-dose fasting, single-dose post-prandial and multiple dose) comparing its test product Carbidopa and Levodopa Extended Release Tablets, 50 mg/200 mg to the reference listed product, Merck Sharp & Dohme's Sinemet® Extended Release Tablets, 50 mg/200 mg.

2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated December 10,1997, ANDA #75-091) due to deficiencies regarding the dissolution data.

### DEFICIENCY COMMENT #1:

The firm was asked to submit complete dissolution profiles generated in different buffered media, in the pH ranges: 1-1.5, 4-4.5, 6-6.5 and 7-7.5.

### THE FIRM'S RESPONSE TO COMMENT #1

The dissolution testing for the test and reference products are summarized below:

| | |
|---|---|
| Method: | USP 23 apparatus II (paddle) at 50 rpm |
| Medium: | 900 mL of 0.1N HCl (pH 1.0 ± 0.1) |
| Number of Tablets: | 12 |
| Test products: | Mylan's Carbidopa/Levodopa ER Tablets, lot #2C012B |

Reference products: Sinemet® CR Tablets

The dissolution testing results are presented in the following table.

**Table. In Vitro Dissolution Testing**

Drug (Generic Name): Carbidopa/Levodopa ER Tablet
Dose Strength: 50 mg/200 mg
ANDA No.: 75-091
Firm: Mylan Pharmaceuticals Inc.
Submission Date: January 23 1998
File Name: 75091a.397

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of 0.1N HCl
Reference Drug: Merck Sharp & Dohme's Sinemet® ER Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

| Sampling Times (Minutes) | Test Product Carbidopa Lot #2C012B Whole Tablet Strength(mg) 50 | | | Reference Product Carbidopa Lot #A6735 Whole Tablet Strength(mg) 50 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 30 | 25 | | 15 | 39 | | 15 |
| 60 | 44 | | 16 | 61 | | 17 |
| 150 | 81 | | 11 | 88 | | 10 |
| 240 | 93 | | 6 | 90 | | 8 |

| Sampling Times (Minutes) | Test Product Levodopa Lot #2C012B Whole Tablet Strength(mg) 200 | | | Reference Product Levodopa Lot #A6735 Whole Tablet Strength(mg) 200 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 30 | 26 | | 15 | 40 | | 11 |
| 60 | 48 | | 15 | 67 | | 9 |
| 150 | 87 | | 9 | 98 | | 3 |
| 240 | 101 | | 4 | 99 | | 2 |

| Sampling Times (Minutes) | Test Product Carbidopa Lot #2C012B Half-Tablet Strength(mg) 50 | | | Reference Product Carbidopa Lot #H6863 Half-Tablet Strength(mg) 50 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 30 | 28 | | 17 | 55 | | 15.6 |
| 60 | 48 | | 17 | 84 | | 13.2 |
| 120 | 77 | | 14 | -- | | -- |
| 150 | 86 | | 11 | 108 | | 4.8 |
| 240 | 94 | | 5 | 109 | | 4.0 |

| Sampling Times (Minutes) | Test Product Levodopa Lot #2C012B Half-Tablet Strength(mg) 200 | | | Reference Product Levodopa Lot #H6863 Half-Tablet Strength(mg) 200 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 30 | 28 | | 18 | 53 | | 15.9 |
| 60 | 49 | | 18 | 83 | | 13.2 |
| 120 | 79 | | 14 | -- | | -- |
| 150 | 89 | | 11 | 108 | | 4.9 |
| 240 | 98 | | 5 | 110 | | 3.8 |

The dissolution data for the test and reference listed products are acceptable.

**The firm's response to comment #1 is acceptable.**

DEFICIENCY COMMENT #2:

Since Carbidopa and Levodopa ER tablets are scored, dissolution profiles for half tablets are required in an addition to whole tablets.

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT #2

The firm submitted the dissolution data profiles for Carbidopa and Levodopa half tablets.

**The firm's response to comment #2 is acceptable.**

**COMMENTS:**

1. The three in vivo bioequivalence studies, single-dose fasting (Protocol #952015, Mylan Protocol #CBLV-9566), single-dose non-fasting (Protocol #952016, Mylan Protocol #CBLV-9567), and steady-state multiple-dose (Protocol #952017, Mylan Protocol #CBLV-9573) conducted by Mylan Pharmaceuticals Inc., on the test product, 50 mg/200 mg Carbidopa and Levodopa ER tablet, lot #2C012B, comparing it to the reference listed drug Merck Sharp & Dohme's Sinemet® CR 50 mg/200 mg tablet, lot #A6735, have been found acceptable. Under fasting conditions, the 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the acceptable range of 80-125%. Under non-fasting conditions, the ratios of the test mean to the reference mean for the AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25. Under steady-state conditions, the 90% confidence intervals for the log-transformed AUC(72-80) and Cmax are within the acceptable range of 80-125% for Carbidopa and Levodopa.

2. The firm conducted in vitro dissolution testing for its test product Carbidopa and Levodopa ER tablets 50 mg/200 mg in the media 0.1N HCl (pH 1.0 ± 0.1). The dissolution apparatus studies used apparatus II at 50 rpm and 75 rpm and apparatus I at 100 rpm. Higher agitation force resulted in faster dissolution leading to the conclusion that the dosage form is sensitive to agitation force. Mylan's degradation study on Carbidopa found that Carbidopa decomposed to methyldopa and an unknown compound in oxidizing or aqueous solutions with pH values higher than 4.0.

   The dissolution testing in 900 mL of 0.1N HCl (pH 1.0 ± 0.1) using apparatus II at 50 rpm is acceptable.

**RECOMMENDATIONS**

1. The three in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, and steady-state multiple-dose conditions conducted by Mylan Pharmaceuticals Inc. on its Carbidopa and Levodopa, 50 mg/200 mg extended release (ER) Tablet, lot #2C012B, comparing it to Merck Sharp & Dohme's Sinemet® CR 50 mg/200 mg tablet have been found acceptable. The three studies demonstrate that under fasting, non-fasting and steady-state conditions, Mylan's Carbidopa and Levodopa, 50 mg/200 mg extended release (ER) Tablet are bioequivalent to Merck Sharp & Dohme's

Sinemet® CR 50 mg/200 mg tablet.

2. The dissolution testing conducted by Mylan Pharmaceuticals Inc., on its Carbidopa and Levodopa, 50 mg/200 mg extended release (ER) Tablet, lot #2B012B is acceptable. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data the following tentative specifications are recommended for Carbidopa and Levodopa:

Whole Tablet

| | |
|---|---|
| 0.5 | hour |
| 1.0 | hour |
| 2.5 | hours |
| 4 | Hours |

Half Tablet

| | |
|---|---|
| 0.5 | hour |
| 1.0 | hour |
| 2.5 | hours |
| 4 | Hours |

The firm should be informed of the above recommendations.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT BZW 6/25/98
FT INITIALLED BDAVIT Barbara McDavit 6/26/98

Concur: Dale P. Conner Date: 6/30/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

**Carbidopa & Levodopa ER Tablets**
50 mg/200 mg
ANDA #75-091
Reviewer: Z.Z. Wahba
File #75091sd.397

**Mylan Pharmaceuticals Inc.**
Morgantown, WV
Submission Date:
March 13, 1997

# REVIEW OF THREE IN VIVO BIOEQUIVALENCE STUDIES, AND IN VITRO DISSOLUTION TESTING DATA

## I. OBJECTIVE:

To review:

1. Mylan's three in vivo bioequivalence studies (single-dose fasting, single-dose post-prandial and multiple dose) comparing its test product Carbidopa and Levodopa Extended Release Tablets, 50 mg/200 mg to the reference listed product, Merck Sharp & Dohme's Sinemet® Extended Release Tablets, 50 mg/200 mg.

2. Dissolution profiles comparing Mylan's Carbidopa and Levodopa Extended Release Tablets, 50 mg/200 mg to the reference listed drug Merck Sharp & Dohme's Sinemet® Extended Release Tablets, 50 mg/200 mg.

**Studies Included in Submission:**

1. A two-way crossover, single-dose bioequivalence study of Carbidopa and Levodopa Extended Release Tablets, 50 mg/200 mg under fasting conditions (Protocol #952015, Mylan Protocol #CBLV-9566).

2. A three-way crossover, single-dose, post-prandial bioequivalence study of Carbidopa and Levodopa Extended Release Tablets, 50 mg/200 mg (Protocol #952016, Mylan Protocol #CBLV-9567).

3. A two-way crossover, steady-state, multiple-dose bioequivalence study of Carbidopa and Levodopa Extended Release Tablets, 50 mg/200 mg (Protocol #952017, Mylan Protocol #CBLV-9573).

## II. BACKGROUND:

Levodopa is the levorotatory isomer of dihydroxyphenylalanine and the metabolic precursor of dopamine. The drug is used in the

treatment of Parkinsonian syndrome. Levodopa is commercially available alone or in combination with carbidopa. Carbidopa is a decarboxylase inhibitor which inhibits decarboxylation of levodopa to dopamine. Concurrent administration of carbidopa inhibits the peripheral decarboxylation of levodopa without affecting the metabolism of the drug within the CNS. Thus, more levodopa is available for transport to the brain.

Levodopa is rapidly and well absorbed from the GI tract. About 40-70% of carbidopa dose is absorbed following oral administration. Although levodopa does not appear to enhance the absorption of carbidopa, carbidopa may enhance the absorption of levodopa by suppressing the metabolism of levodopa in the GI tract. Plasma levodopa concentrations are increased when carbidopa and levodopa are administered concomitantly, principally because of inhibition by carbidopa of the peripheral metabolism of levodopa.
Levodopa is widely distributed into most body tissues and the total volume of distribution is about 65% of body weight. Probably less than 1% of absorbed levodopa penetrates the CNS and only a small amount enters the brain. Therefore, large doses of levodopa are required for adequate therapeutic effect and these may often be accompanied by nausea and other adverse reactions. Carbidopa is also widely distributed into most body tissues; however, it does not cross the blood-brain barrier.

The plasma half-life of levodopa is approximately 1 hour. The plasma half-life of carbidopa is 1-2 hours. When carbidopa and levodopa are administered concurrently, the plasma half-life of levodopa is increased to about 2 hours. Most of the absorbed levodopa is decarboxylated to dopamine and small amounts of levodopa are metabolized to norepinephrine, epinephrine, 3-methoxytyramine, and 3-O-methyldopa. Dopamine is further metabolized to 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) and excreted in urine. Carbidopa is not extensively metabolized. When carbidopa and levodopa are administered concurrently, 60% of unchanged levodopa excreted in urine.

Levodopa is commercially available alone in three strengths: 100 mg, 250 mg and 500 mg tablets. Carbidopa and levodopa combination tablets are commercially available in three strengths: 10 mg/100 mg, 25 mg/100 mg, 25 mg/250 mg and as sustained-release 50 mg/200 mg SinemetR CR (Merck Sharp & Dohme).

## III. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER FASTING CONDITIONS (Protocol #952015, Mylan Protocol #CBLV-9566)

**A. Sponsor:**

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26505

**Study site**
**Clinical and Analytical Facilities**
Phoenix International Life Sciences Inc.
2350 Cohen Street
Quebec, Canada

Principle Investigator:
Pierre Geoffroy, M.D. Medical Director
Richard Lalonde, Pharm.D. Scientific Director

Clinical Study Dates:
Phase I: August 04-05, 1996
Phase II: August 11-12, 1996
Analytical Study Dates:
August 26, 1996 - September 26, 1996

**B. Study design:**

Randomized, single dose, two-way crossover study, under fasting conditions.

**C. Subjects:**

Forty-four (44) healthy male subjects (plus 4 alternates) were enrolled and completed the study. Samples of the first forty-four subjects were analyzed as per protocol. The subjects were in the range of 18 to 45 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

**Subject Selection Criteria:**

Only medically healthy subjects as determined by normal history, physical examination, laboratory profiles and ECG were enrolled in the study.

**Subject Exclusion Criteria:**

Subjects were excluded from the study based on the following

criteria:

- A history of asthma, angioedema, hypertension, cardiovascular, renal, gastrointestinal, hepatic, endocrine, neurological or hematological disease.
- A history of hypersensitivity or idiosyncratic reaction to carbidopa, levodopa or any other anti-Parkinsonian drugs.
- A history of drug or alcohol addiction or abuse.
- Use of any medication known to alter hepatic enzyme activity within 30 days prior to entry into this study.
- A minimum screening and/or check-in blood pressure of 100/60 mmHg and minimum plus rate of 60 bpm.

Subject Restrictions:

- No subject took any medications, including OTC products for at least two weeks prior to the beginning of the study and until completion of the study.
- No alcoholic, xanthine and caffeine containing foods and beverages were allowed, beginning with 24 hours prior to dosing and until completion of the study.

**D. Treatment Plan:**

Test Product: 1 X 50 mg/200 mg Mylan's Carbidopa and Levodopa Extended Release Tablet; Lot #2C012B; Batch size tablets; assay potency 96.8% for carbidopa and 100.2% for levodopa; content uniformity 96.6% for carbidopa and 100.1% for levodopa; manufacturing date 3/7/96.

Reference Product: 1 X 50 mg/200 mg Merck Sharp & Dohme's Sinemet® Extended Release Tablets; Lot #A6735; assay potency 99.9% for carbidopa and 100.0% for levodopa; content uniformity 98.3% for carbidopa and 99.2% for levodopa; expiration date: 1/98.

Washout period: one week between doses.

**E. Drug, Food and Fluid Intake:**

Subjects fasted overnight (10 hours) before dosing and for 5 hours thereafter. Water ad libitum was allowed until 1 hour before dosing and 1 hour after dosing. The subjects received their medication with 240 mL of water. Standard meals were provided at appropriate times thereafter (lunch at 5 hours, supper at 10 hours post-dose).

F. **Blood sampling:**

Blood samples: Blood samples were collected at 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16 and 24 hours post-dose. The plasma samples were extracted and stored frozen at -80 °C until analysis.

G. **ASSAY METHODOLOGY**:

1. Methods:
The plasma samples were analyzed for carbidopa and levodopa by

The assay validation data are summarized as follows:

2. Linearity: (Vol.C1.3, p 807)
The assay was linear for the concentration range of:
4.04 to 201.92 ng/mL for carbidopa
20.0 to 2106.0 ng/mL for levodopa

3. Sensitivity:
The limit of quantitation (LOQ) was 4.11 ng/mL and 20.2 ng/mL for carbidopa and levodopa, respectively.

4. Accuracy and Precision Validation: (Vol.C1.3, pp 759-813)
The following quality control concentrations for carbidopa (5.9, 19.67, 83.59, 157.35 ng/mL), and levodopa (24.68, 74.04, 839.17, 1579.61 ng/mL) were used to evaluate the validation of the analytical method.
The following values represent the average mean of control samples.

| Precision: (CV% range) | Between-batch | Within-batch |
|---|---|---|
| Carbidopa | 3.7-9.8% | 3.1-5.7% |
| Levodopa | 2.2-4.8% | 0.9-3.3% |

| Accuracy: (% range) | Between-batch | Within-batch |
|---|---|---|
| Carbidopa | 91.4-98.8% | 88.3-98.6% |
| Levodopa | 96.7-100.4% | 97.9-101.8% |

5. Recovery: (vol.C1.3, pp 775-776)
The following values represent the average mean of recovery of control samples from plasma. The mean recovery for carbidopa in human plasma was 33.2%, 32.8% and 32.5% for 19.67, 83.39 and 157.35 ng/mL, respectively. The mean recovery for levodopa in human plasma was 76.4%, 78.7% and 79.4% for 74.04,

839.17 and 1579.61 ng/mL, respectively.

6. Stability: (vol. C1.3, pp 783-793)

a. Freeze-Thaw:
Carbidopa and levodopa were stable after two freeze-thaw cycles in human plasma. Levodopa was also stable after 3 freeze-thaw cycles in human plasma, but failed for carbidopa.

b. Short term stability:
Stability on the bench (in ice bath): Carbidopa and levodopa were stable for 3.5 hours and 5.0 hours, respectively.
Wet extract stability: Carbidopa and levodopa were stable for 95 hours and 120 hours, respectively.

b. Long term stability:
Carbidopa and levodopa were stable for a maximum of 123 days in human plasma at -80°C.

**H. Safety Monitoring:**
Vital signs including blood pressure, pulse, temperature and respiration were obtained prior to drug administration (0 hour) and at 1, 2, 4, 8 and 12 hours post-dose.

**I. In Vivo Data Analysis:**
Forty-four (44) healthy male subjects (plus 4 alternates) were enrolled and completed the study. Samples of the first forty-four subjects were analyzed as per protocol (subject #1-44).

Adverse Events:
Subject #28 was examined by a physician as he experienced an episode of trembling and fainting 11.8 hours and 13.7 hours after Period 2 dosing (Treatment A), respectively. Subject #28 was prescribed Clavulin® (amoxicillin-clavulanate potassium) to alleviate discomfort. Subject #30 felt heart palpitations 16.7 hours after Period 2 dosing (Treatment A). Subject #40 had loose stools 7.9 hours after Period 2 dosing (Treatment B). There were no serious or life threatening medical events reported for this study. No subjects were dropped or withdrawn due to medical events.

The pharmacokinetic parameters of carbidopa and levodopa were

analyzed using SAS-GLM procedure for analysis of variance. Plasma carbidopa and levodopa levels, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

**Table #1**

**Mean Plasma Concentrations of Carbidopa (ng/mL) in 44 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), Under Fasting Conditions**

**(Test Lot #2C012B, Reference Lot #A6735)**

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| TIME HR | | | | | |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | . |
| 0.25 | 0.36 | 1.38 | 0.28 | 1.30 | 1.32 |
| 0.5 | 9.01 | 10.94 | 8.10 | 6.82 | 1.11 |
| 0.75 | 25.62 | 23.51 | 24.17 | 16.81 | 1.06 |
| 1 | 45.94 | 31.27 | 42.49 | 23.78 | 1.08 |
| 1.5 | 78.11 | 44.34 | 75.89 | 37.79 | 1.03 |
| 2 | 107.82 | 58.66 | 110.19 | 55.02 | 0.98 |
| 2.5 | 124.90 | 61.64 | 134.67 | 67.19 | 0.93 |
| 3 | 136.49 | 62.44 | 144.94 | 71.90 | 0.94 |
| 3.5 | 141.28 | 76.25 | 152.01 | 85.42 | 0.93 |
| 4 | 150.85 | 91.22 | 152.15 | 89.62 | 0.99 |
| 5 | 133.24 | 72.20 | 157.14 | 84.77 | 0.85 |
| 6 | 122.74 | 74.64 | 132.36 | 70.95 | 0.93 |
| 8 | 51.73 | 33.29 | 55.59 | 33.15 | 0.93 |
| 10 | 21.70 | 12.89 | 24.53 | 16.00 | 0.88 |
| 12 | 10.89 | 5.45 | 11.85 | 6.45 | 0.92 |
| 14 | 5.98 | 4.49 | 6.09 | 3.84 | 0.98 |
| 24 | 0.11 | 0.74 | 0.00 | 0.00 | . |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

**Table #2**

**Mean Pharmacokinetic Parameters (Arithmetic) for Carbidopa in 44 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), Under Fasting Conditions**

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI | 950.61 | 432.20 | 1015.20 | 450.89 | 0.94 |
| AUCT | 924.07 | 430.33 | 991.22 | 447.47 | 0.93 |
| CMAX | 179.32 | 94.27 | 187.98 | 93.72 | 0.95 |
| KE | 0.32 | 0.12 | 0.31 | 0.07 | 1.03 |
| THALF | 2.49 | 1.44 | 2.34 | 0.58 | 1.07 |
| TMAX | 4.05 | 1.23 | 4.06 | 1.22 | 1.00 |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

## Table #3
## LSMeans And The 90% Confidence Intervals For Carbidopa (Under Fasting Conditions)

| | LSM1 | LSM2 | RLSM12 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| LAUCI | 861.49 | 922.91 | 0.93 | 82.82 | 105.21 |
| LAUCT | 832.30 | 898.07 | 0.93 | 81.87 | 104.91 |
| LCMAX | 160.31 | 168.29 | 0.95 | 84.38 | 107.54 |

UNIT: AUC=NG HR/ML CMAX=NG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

1. The mean plasma carbidopa levels reached a maximum level of concentration between 4-5 hours (Table #1 and Figures #1&2).

2. The pharmacokinetic parameters AUCt, AUCi and Cmax for test product are comparable to the reference listed product as shown in Table #2. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3).
There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCt, AUCi and Cmax.

## Table #4
## Mean Plasma Concentrations of Levodopa (ng/mL) in 44 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), Under Fasting Conditions
## (Test Lot #2C012B, Reference Lot #A6735)

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| TIME HR | | | | | |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | . |
| 0.25 | 71.84 | 133.05 | 59.70 | 89.09 | 1.20 |
| 0.5 | 393.47 | 262.02 | 388.46 | 303.07 | 1.01 |
| 0.75 | 507.06 | 273.84 | 482.88 | 270.77 | 1.05 |
| 1 | 662.27 | 322.20 | 613.97 | 301.20 | 1.08 |
| 1.5 | 828.39 | 289.73 | 785.23 | 299.95 | 1.05 |
| 2 | 902.72 | 292.12 | 824.15 | 309.97 | 1.10 |
| 2.5 | 861.35 | 214.83 | 816.38 | 277.60 | 1.06 |
| 3 | 822.08 | 205.31 | 750.74 | 215.92 | 1.10 |
| 3.5 | 705.32 | 167.54 | 662.90 | 198.03 | 1.06 |
| 4 | 629.23 | 221.44 | 597.59 | 153.30 | 1.05 |
| 5 | 412.87 | 160.30 | 480.30 | 162.14 | 0.86 |
| 6 | 269.63 | 153.73 | 305.38 | 137.02 | 0.88 |
| 8 | 98.87 | 47.68 | 117.64 | 65.07 | 0.84 |
| 10 | 42.56 | 30.19 | 48.61 | 27.52 | 0.88 |

| | | | | | |
|---|---|---|---|---|---|
| 12 | 7.17 | 16.12 | 7.96 | 13.91 | 0.90 |
| 14 | 2.53 | 8.28 | 0.50 | 3.33 | 5.04 |
| 24 | 0.00 | 0.00 | 0.00 | 0.00 | . |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

**Table #5**

**Mean Pharmacokinetic Parameters (Arithmetic) for Levodopa in 44 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), Under Fasting Conditions**

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI | 4182.74 | 718.46 | 4160.13 | 696.57 | 1.01 |
| AUCT | 4109.23 | 715.49 | 4081.08 | 697.41 | 1.01 |
| CMAX | 1084.98 | 247.32 | 1043.83 | 316.06 | 1.04 |
| KE | 0.46 | 0.06 | 0.47 | 0.05 | 0.98 |
| THALF | 1.52 | 0.18 | 1.49 | 0.17 | 1.02 |
| TMAX | 2.19 | 0.89 | 2.07 | 1.02 | 1.05 |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

**Table #6**

**LSMeans And The 90% Confidence Intervals For Levodopa (Under Fasting Conditions)**

| | LSM1 | LSM2 | RLSM12 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| LAUCI | 4124.72 | 4102.73 | 1.01 | 97.32 | 103.85 |
| LAUCT | 4050.58 | 4022.55 | 1.01 | 97.44 | 104.07 |
| LCMAX | 1060.67 | 1000.05 | 1.06 | 98.33 | 114.40 |

UNIT: AUC=NG HR/ML CMAX=NG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

1. The mean plasma levodopa levels reached maximum concentration around 2.0 hours (Table #4 and Figure #3&4).

2. The pharmacokinetic parameters AUCt, AUCi and Cmax for test product are comparable to the reference listed product as shown in Table #5. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #6).
   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCt, AUCi and Cmax.

## IV. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER NON-FASTING CONDITIONS (Protocol #952016, Mylan Protocol #CBLV-9567)

**A. Sponsor:**

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26505

**Study site**
**Clinical and Analytical Facilities**
Phoenix International Life Sciences Inc.
2350 Cohen Street
Quebec, Canada

Principle Investigator:
Pierre Geoffroy, M.D. Medical Director

Study Dates:
Phase I: August 31, 1996 - September 01, 1996
Phase II: September 7, 1996 -September 08, 1996
Phase III: September 14, 1996 - September 15, 1996

Analytical Study Dates:
September 19, 1996 - October 21, 1996

**B. Study design:**

Randomized, three-way single dose crossover study, under non-fasting conditions.

**C. Subjects:**

Eighteen (18) healthy male subjects were enrolled but only 17 completed all periods of the clinical study. Subject #1 elected to withdraw from the study 6 days after period 2 dosing for personal reasons that were not study related.

**D. Treatment Plan:**

**Treatment A: Fasting conditions**, 1 X 50 mg/200 mg Mylan's Carbidopa and Levodopa Extended Release Tablet; Lot #2C012B; Batch size [redacted] tablets; assay potency 96.8% for carbidopa and 100.2% for levodopa; content uniformity 96.6% for carbidopa and 100.1% for levodopa; manufacturing date 3/7/96.

**Treatment B: Non-fasting condition**, 1 X 50 mg/200 mg Mylan's

Carbidopa and Levodopa Extended Release Tablet; Lot #2C012B; Batch size ablets; assay potency 96.8% for carbidopa and 100.2% for levodopa; content uniformity 96.6% for carbidopa and 100.1% for levodopa; manufacturing date 3/7/96.

**Treatment C: Non-fasting conditions**, 1 X 50 mg/200 mg Merck's Sinemet® Extended Release Tablets; Lot #A6735; assay potency 99.9% for carbidopa and 100.0% for levodopa; content uniformity 98.3% for carbidopa and 99.2% for levodopa; expiration date: 1/98.

**Washout period:** one week between doses.

**E. Drug, Food and Fluid Intake:**

Subjects who received treatment A, fasted overnight for 10 hours before dosing and for 5 hours after each drug administration. Subjects who received treatments B and C, fasted overnight for 9.5 hours before they were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. Each dose was followed by 180 mL of room temperature tap water according to randomized dosing schedule. Water was allowed ad lib except for 1 hour before dosing and until 2 hours after dosing. Standard meals were provided at appropriate times thereafter (lunch at 5 hours, supper at 10 hours post-dose).

**F. Blood sampling:**

Blood samples: Blood samples were collected at 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16 and 24 hours post-dose. The plasma samples were extracted and stored frozen at -80 °C until analysis.

**G. Assay Methodology:**

The same as Protocol #952015 - Mylan Protocol #CBLV-9566; under fasting conditions.

Accuracy and Precision: (Vol.C1.7, pp 2300-2301)
The following values represent the average mean of quality control samples.

| Precision: (CV% range) | Between-day | Within-day |
|---|---|---|
| Carbidopa | 5.0-6.5% | 3.0-5.7% |
| Levodopa | 2.3-3.8% | 0.9-5.2% |

| Accuracy: (% range) | Between-batch | Within-batch |
|---|---|---|
| Carbidopa | 96.7-101.8% | 88.3-113.3% |
| Levodopa | 97.6-100.4% | 97.9-101.8% |

**H. Data Analysis:**

Eighteen (18) healthy male subjects were enrolled but only 17 completed all periods of the clinical study (subjects #2-18). Subject #1 elected to withdraw from the study 6 days after period 2 dosing for personal reasons that were not study related.

Adverse Events: Subject #8 felt nauseated 1.8 and 3.9 hours after period 2 dosing (treatment A). Subject #9 felt dizzy 1.7 hours after period 2 dosing (treatment A). No serious medical events were reported during the study and no medication was required for any events.

The pharmacokinetic parameters of carbidopa and levodopa were analyzed using SAS-GLM procedure for analysis of variance. Plasma carbidopa and levodopa levels, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

**Table #7**
**Mean Plasma Concentrations of Carbidopa (ng/mL) in 17 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), Under Non-Fasting Conditions**
**(Test Lot #2C012B, Reference Lot #A6735)**

| | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 | SD3 | RMEAN12 |
|---|---|---|---|---|---|---|---|
| TIME HR | | | | | | | |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | . |
| 0.25 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | . |
| 0.5 | 9.02 | 9.39 | 0.31 | 1.27 | 0.00 | 0.00 | 29.38 |
| 0.75 | 26.64 | 22.98 | 1.73 | 3.64 | 2.27 | 3.89 | 15.41 |
| 1 | 43.34 | 35.51 | 5.33 | 6.17 | 8.07 | 7.73 | 8.13 |
| 1.5 | 73.78 | 45.11 | 21.98 | 19.51 | 25.78 | 23.38 | 3.36 |
| 2 | 90.29 | 44.20 | 47.43 | 32.61 | 44.92 | 38.92 | 1.90 |
| 2.5 | 111.74 | 48.33 | 71.17 | 48.51 | 61.56 | 46.16 | 1.57 |
| 3 | 117.73 | 46.90 | 86.37 | 47.37 | 81.54 | 53.99 | 1.36 |
| 3.5 | 127.38 | 50.44 | 94.62 | 51.28 | 83.21 | 35.04 | 1.35 |
| 4 | 126.28 | 52.93 | 96.14 | 48.70 | 96.23 | 53.34 | 1.31 |
| 5 | 117.41 | 42.09 | 77.06 | 36.60 | 82.69 | 37.65 | 1.52 |
| 6 | 111.69 | 58.69 | 75.83 | 35.11 | 76.71 | 31.31 | 1.47 |
| 8 | 71.62 | 53.61 | 33.93 | 14.63 | 36.53 | 16.34 | 2.11 |
| 10 | 28.99 | 24.89 | 15.06 | 7.28 | 17.00 | 10.19 | 1.93 |
| 12 | 13.21 | 10.75 | 6.76 | 4.15 | 7.68 | 4.70 | 1.95 |
| 14 | 5.68 | 5.07 | 2.54 | 3.27 | 2.40 | 3.49 | 2.23 |
| 24 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | . |

(CONTINUED)

| | RMEAN13 | RMEAN23 |
|---|---|---|
| TIME HR | | |
| 0 | . | . |
| 0.25 | . | . |
| 0.5 | . | . |
| 0.75 | 11.76 | 0.76 |
| 1 | 5.37 | 0.66 |
| 1.5 | 2.86 | 0.85 |
| 2 | 2.01 | 1.06 |
| 2.5 | 1.82 | 1.16 |
| 3 | 1.44 | 1.06 |
| 3.5 | 1.53 | 1.14 |
| 4 | 1.31 | 1.00 |
| 5 | 1.42 | 0.93 |
| 6 | 1.46 | 0.99 |
| 8 | 1.96 | 0.93 |
| 10 | 1.71 | 0.89 |
| 12 | 1.72 | 0.88 |
| 14 | 2.37 | 1.06 |
| 24 | . | . |

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed
RMEAN23=T/R ratio under non-fasting conditions

## Table #8

## Mean Pharmacokinetic Parameters (Arithmetic) for Carbidopa in 17 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), Under Non-Fasting Conditions

| | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 | SD3 | RMEAN12 |
|---|---|---|---|---|---|---|---|
| PARAMETER | | | | | | | |
| AUCI | 916.82 | 372.99 | 554.24 | 150.10 | 559.68 | 169.50 | 1.65 |
| AUCT | 896.78 | 365.72 | 536.64 | 150.09 | 542.93 | 166.99 | 1.67 |
| CMAX | 154.31 | 55.25 | 125.00 | 33.88 | 116.47 | 50.72 | 1.23 |
| KE | 0.39 | 0.09 | 0.36 | 0.06 | 0.39 | 0.08 | 1.08 |
| *LAUCI | 844.84 | 0.43 | 535.62 | 0.27 | 539.27 | 0.28 | 1.58 |
| *LAUCT | 825.26 | 0.43 | 517.35 | 0.28 | 522.22 | 0.28 | 1.60 |
| *LCMAX | 144.70 | 0.38 | 120.96 | 0.26 | 108.55 | 0.37 | 1.20 |
| THALF | 1.87 | 0.39 | 1.98 | 0.36 | 1.83 | 0.36 | 0.94 |
| TMAX | 4.21 | 1.57 | 4.15 | 1.40 | 4.56 | 1.29 | 1.01 |

(CONTINUED)

| | RMEAN13 | RMEAN23 |
|---|---|---|
| PARAMETER | | |
| AUCI | 1.64 | 0.99 |
| AUCT | 1.65 | 0.99 |
| CMAX | 1.32 | 1.07 |
| KE | 0.98 | 0.91 |
| *LAUCI | 1.57 | 0.99 |
| *LAUCT | 1.58 | 0.99 |
| *LCMAX | 1.33 | 1.11 |
| THALF | 1.02 | 1.08 |
| TMAX | 0.92 | 0.91 |

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed
RMEAN23=T/R ratio under non-fasting conditions
* The values represent the geometric mean (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma levels for carbidopa reached the maximum around 3.5-4 hours (Table #7 and Figures #5&6).

2. Under non-fasting conditions, the T/R mean ratios (RMEAN2/3) for log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.80 to 1.25 that has been set by the Division of Bioequivalence (Table #8).

3. For the test product, the mean LAUCt, LAUCi and LCmax values after dosing with food decreased by 37.3%, 36.6% and 16.4%, respectively, of the values reported in the fasting state.

**Table #9**
**Mean Plasma Concentrations of Levodopa (ng/mL) in 17 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), Under Non-Fasting Conditions**
**(Test Lot #2C012B, Reference Lot #A6735)**

| | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 | SD3 | RMEAN12 |
|---|---|---|---|---|---|---|---|
| TIME HR | | | | | | | |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | . |
| 0.25 | 105.79 | 177.06 | 5.11 | 21.08 | 2.12 | 8.73 | 20.70 |
| 0.5 | 399.89 | 209.74 | 19.02 | 46.17 | 34.64 | 55.50 | 21.02 |
| 0.75 | 412.89 | 171.94 | 81.78 | 128.05 | 137.46 | 175.22 | 5.05 |
| 1 | 519.26 | 153.06 | 190.94 | 258.72 | 216.75 | 251.75 | 2.72 |
| 1.5 | 733.12 | 314.58 | 442.29 | 335.18 | 433.87 | 367.66 | 1.66 |
| 2 | 818.56 | 216.45 | 725.89 | 560.06 | 575.19 | 364.12 | 1.13 |
| **2.5** | **929.79** | 326.04 | **875.51** | 532.46 | 650.83 | 325.33 | 1.06 |
| 3 | 829.51 | 272.67 | 833.88 | 397.13 | **822.78** | 382.98 | 0.99 |
| 3.5 | 678.29 | 258.30 | 723.82 | 297.05 | 786.75 | 318.69 | 0.94 |
| 4 | 554.89 | 209.91 | 663.43 | 290.29 | 736.66 | 242.27 | 0.84 |
| 5 | 363.46 | 129.91 | 516.48 | 196.18 | 559.64 | 204.46 | 0.70 |
| 6 | 234.83 | 111.06 | 460.69 | 358.89 | 455.65 | 348.45 | 0.51 |
| 8 | 93.37 | 60.82 | 152.85 | 108.42 | 157.31 | 109.74 | 0.61 |
| 10 | 37.70 | 32.74 | 63.13 | 58.76 | 79.01 | 88.83 | 0.60 |
| 12 | 6.96 | 18.28 | 19.60 | 34.52 | 25.81 | 39.24 | 0.36 |
| 14 | 2.14 | 8.83 | 6.08 | 14.27 | 5.94 | 16.93 | 0.35 |
| 24 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | . |

(CONTINUED)

| | RMEAN13 | RMEAN23 |
|---|---|---|
| TIME HR | | |
| 0 | . | . |
| 0.25 | 49.96 | 2.41 |
| 0.5 | 11.54 | 0.55 |
| 0.75 | 3.00 | 0.59 |
| 1 | 2.40 | 0.88 |
| 1.5 | 1.69 | 1.02 |
| 2 | 1.42 | 1.26 |
| 2.5 | 1.43 | 1.35 |
| 3 | 1.01 | 1.01 |
| 3.5 | 0.86 | 0.92 |
| 4 | 0.75 | 0.90 |
| 5 | 0.65 | 0.92 |
| 6 | 0.52 | 1.01 |
| 8 | 0.59 | 0.97 |
| 10 | 0.48 | 0.80 |
| 12 | 0.27 | 0.76 |
| 14 | 0.36 | 1.02 |
| 24 | . | . |

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed
RMEAN23=T/R ratio under non-fasting conditions

## Table #10
## Pharmacokinetic Parameters Levodopa in 17 Subjects Following Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), Under Non-Fasting Conditions

| | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 | SD3 | RMEAN12 |
|---|---|---|---|---|---|---|---|
| PARAMETER | | | | | | | |
| AUCI | 3868.16 | 1005.28 | 4124.11 | 744.00 | 4133.80 | 673.65 | 0.94 |
| AUCT | 3799.39 | 993.53 | 4052.81 | 738.84 | 4053.37 | 657.38 | 0.94 |
| CMAX | 1079.89 | 292.77 | 1222.01 | 359.25 | 1144.28 | 260.02 | 0.88 |
| KE | 0.47 | 0.06 | 0.49 | 0.08 | 0.47 | 0.06 | 0.95 |
| *LAUCI | 3755.62 | 0.25 | 4065.82 | 0.17 | 4086.72 | 0.15 | 0.92 |
| *LAUCT | 3687.28 | 0.25 | 3994.17 | 0.17 | 4007.76 | 0.15 | 0.92 |
| *LCMAX | 1040.40 | 0.29 | 1177.00 | 0.28 | 1115.94 | 0.24 | 0.88 |
| THALF | 1.50 | 0.24 | 1.44 | 0.23 | 1.48 | 0.19 | 1.05 |
| TMAX | 2.13 | 0.82 | 3.35 | 1.48 | 3.53 | 1.26 | 0.64 |

(CONTINUED)

| | RMEAN13 | RMEAN23 |
|---|---|---|
| PARAMETER | | |
| AUCI | 0.94 | 1.00 |
| AUCT | 0.94 | 1.00 |
| CMAX | 0.94 | 1.07 |
| KE | 0.99 | 1.04 |
| *LAUCI | 0.92 | 0.99 |
| *LAUCT | 0.92 | 1.00 |
| *LCMAX | 0.93 | 1.05 |
| THALF | 1.01 | 0.97 |
| TMAX | 0.60 | 0.95 |

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed
RMEAN23=T/R ratio under non-fasting conditions
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma levels for levodopa reached the maximum around 2.5-3.0 hours (Table #9 and Figures #7&8).

2. Under non-fasting conditions, the T/R mean ratios (RMEAN2/3) for log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.80 to 1.25 set by the Division of Bioequivalence (Table #10).

## V. MULTIPLE DOSE BIOEQUIVALENCE STUDY

(Protocol #952017, Mylan Protocol #CBLV-9573)

The objective of this study is to compare the bioavailability of Mylan's Carbidopa and Levodopa ER Tablet, 50 mg/200 mg with Merck Sharp & Dohme's Sinemet® CR Tablet, 50 mg /200 mg under steady-state conditions.

### A. Sponsor:

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26505

**Study site**
**Clinical and Analytical Facilities**
Phoenix International Life Sciences Inc.
2350 Cohen Street
Quebec, Canada

Principle Investigator:
Pierre Geoffroy, M.D. Medical Director

Clinical Study Dates:
Phase I: November 07-11, 1996
Phase II: November 18-23, 1996

Analytical Study Dates:

November 26, 1996 - December 18, 1996

**B. Study design:**

Randomized, multiple-dose (every 8 hours for 10 doses in each study phase), steady-state, two-way crossover design, under fasting conditions.

**C. Subjects:**

Forty-four (44) healthy male subjects entered the clinical study but only 38 subjects completed the entire clinical portion of the study. Subjects #22, #29, #41 and #44 were discontinued from the study due to medical events. Subjects 28 and #35 elected to withdraw from the study due to personal reasons that were not study related.

**D. Subject Selection, Exclusion and Restriction Criteria:**

Similar to Protocol #952015, Mylan Protocol #CBLV-9566

**E. Treatment Plan:**

Test Product: 1 X 50 mg/200 mg Mylan's Carbidopa and Levodopa Extended Release Tablet; Lot #2C012B; Batch size tablets; assay potency 96.8% for carbidopa and 100.2% for levodopa; content uniformity 96.6% for carbidopa and 100.1% for levodopa; manufacturing date 3/7/96.

Reference Product: 1 X 50 mg/200 mg Merck's Sinemet® Extended Release Tablets; Lot #A6735; assay potency 99.9% for carbidopa and 100.0% for levodopa; content uniformity 98.3% for carbidopa and 99.2% for levodopa; expiration date: 1/98.

Washout period: one week between doses.

**F. Drug, Food and Fluid Intake:**

**For Days 1-3:** The morning doses followed at least 10 hours of fast (overnight); the afternoon and evening doses were administered approximately 2 hours after a meal or snack.

**For Day 4:** The subjects fasted overnight (for 10 hours) prior to dosing and until 5 hours after dosing on Day-4.

Each dose (test or reference product) was administered with 240 mL of water. Water was restricted 1.0 hour before and 2.0

hours after each dosing except for 240 mL water administered with the dose. Water was permitted ad lib at all other times. Identical meal plans were served to all study subjects for both study periods.

Note: Each formulation (test and reference) was administered each day three times (at 0800, 1600 and 2400 hour for 3 days) and only one dose on Day 4 (at 0800 hour).

**G. Blood samples:**

In each period, blood samples were collected prior to dosing on day 1, 2, 3 and 4 and at: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, and 8 hours after the 72-hour dose. All plasma samples were stored frozen at -80°C until shipment to the laboratory for analysis.

**H. Assay Methodology:**

The same as Protocol #952015 - Mylan Protocol #CBLV-9566; under fasting conditions.

Accuracy and Precision: (Vol.C1.10, pp 3651-3652; vol.C1.11 pp 4306-4309)

The following values represent the average mean of quality control samples.

| Precision: (CV% range) | Between-day | Within-day |
|---|---|---|
| Carbidopa | 4.6-8.3% | 3.0-5.7% |
| Levodopa | 4.5-5.1% | 0.9-5.2% |

| Accuracy: (% range) | Between-batch | Within-batch |
|---|---|---|
| Carbidopa | 94.1-100.5% | 88.3-113.3% |
| Levodopa | 96.4-99.2% | 97.9-101.8% |

**I. Data Analysis:**

Forty-four (44) healthy male subjects entered the clinical study but only 38 subjects completed the entire clinical portion of the study (subjects #1-21, 23-27, 30-34, 36-40 and 42-43). The following subjects were withdrawn from the study due medical events: Subjects #22 (2.8 hours after Dose #2 in Period 1, Test Treatment), #29 (4.7 hours after Dose #1 in Period 1, Test Treatment ), #41 (1.1 hours after Dose#10 in Period 2, Test Treatment) and #44 (7.9 days after Dose #10 in period 1, Test Treatment). The following subjects elected to

withdraw from the study due to personal reason: Subjects #28 (2.9 hours after Dose #8 in Period 2, Reference Treatment) and #35 (7.5 days after Dose #10 in Period 1, Test Treatment).

Adverse Events: (vo. C.10, pp 3762-3763 and 3769-3782) Summary of the medical events are shown in the table below:

| Parameter | Test Treatment (no. Of subjects) | Reference Treatment (no. Of subjects) |
|---|---|---|
| Dizziness | 5 | 1 |
| white spots in front of eyes | 1 | -- |
| Headache | 8 | 12 |
| Pain in lower abdomen | 1 | -- |
| tiredness | 2 | 2 |
| Shaky left or right leg | 2 | -- |
| Rash on some areas of the body | 2 | -- |
| lightheaded | 1 | -- |
| Spasm in or under eye | 2 | -- |
| Nausea | 1 | 3 |
| Stomachache | 1 | 3 |
| Cold shivers | -- | 2 |
| Metallic taste in mouth following dosing | -- | 1 |

There were no serious medical events reported during this study.

Statistical analysis was performed using SAS-GLM. The

statistical differences due to treatment, sequence and period effects were evaluated for plasma carbidopa, levodopa, as well as the following parameters AUCt, Cmax, Cavg, Fluc (fluctuation at steady state) and Tmax. The two one-sided t tests were used to estimate the 90% confidence interval for the AUCt and Cmax. The results are summarized in the Tables below:

**Table #11**

**Mean Plasma Concentrations of Carbidopa at Steady-State (Day-4) in 38 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), every 8 hours for 10 doses (Unit: ng/mL)**

**(Test Lot #2C012B, Reference Lot #A6735)**

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| 0 | 0.0 | | 0.0 | | |
| 24 | 46.8 | 51.8 | 50.9 | 55.0 | 0.20 |
| 48 | 48.2 | 42.6 | 56.2 | 48.5 | 0.04 |
| 72 | 57.71 | 26.99 | 57.49 | 36.59 | 1.00 |
| 72.25 | 51.37 | 25.31 | 54.26 | 32.68 | 0.95 |
| 72.5 | 60.08 | 22.93 | 63.93 | 36.97 | 0.94 |
| 72.75 | 75.67 | 26.00 | 77.77 | 34.23 | 0.97 |
| 73 | 96.48 | 31.84 | 98.46 | 38.49 | 0.98 |
| 73.5 | 123.91 | 38.48 | 136.06 | 50.84 | 0.91 |
| 74 | 144.21 | 46.46 | 153.08 | 55.39 | 0.94 |
| 74.5 | 163.89 | 52.38 | 163.24 | 59.52 | 1.00 |
| 75 | 165.57 | 57.94 | 175.77 | 65.68 | 0.94 |
| 75.5 | 158.83 | 58.05 | 176.58 | 71.74 | 0.90 |
| 76 | 155.06 | 55.14 | 168.18 | 60.86 | 0.92 |
| 76.5 | 144.81 | 55.78 | 163.96 | 64.86 | 0.88 |
| 77 | 139.94 | 58.44 | 156.24 | 66.27 | 0.90 |
| 78 | 127.74 | 67.94 | 142.40 | 70.58 | 0.90 |
| 79 | 88.96 | 49.37 | 98.49 | 59.44 | 0.90 |
| 80 | 54.36 | 31.22 | 64.81 | 44.87 | 0.84 |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

## Table #12
## Arithmetic Mean For Carbidopa at Steady-State (Day-4) in 38 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), every 8 hours for 10 doses (Unit: ng/mL)

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCT | 967.14 | 301.07 | 1052.01 | 353.26 | 0.92 |
| CAVG | 120.89 | 37.63 | 131.50 | 44.16 | 0.92 |
| CMAX | 194.36 | 60.84 | 215.76 | 77.52 | 0.90 |
| CMIN | 36.91 | 13.16 | 43.40 | 29.79 | 0.85 |
| FLUC1 | 1.30 | 0.20 | 1.32 | 0.32 | 0.98 |
| TMAX | 75.36 | 1.41 | 75.55 | 1.25 | 1.00 |

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
AUCT= $AUCT_{72-80}$
CAVG= AUCT/8
CMIN= Minimum measured plasma concentration over the final dosing interval.
FLUC1= [CMAX -CMIN]/CAVG

## Table #13
## LSMEANS AND 90% CONFIDENCE INTERVALS For Carbidopa at Steady-State (Day-4) in 38 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), every 8 hours for 10 doses (Unit: ng/mL)

| | LSM1 | LSM2 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|
| PARAMETER | | | | |
| LAUCT | 922.07 | 993.81 | 84.83 | 101.48 |
| LCAVG | 115.26 | 124.23 | 84.83 | 101.48 |
| LCMAX | 184.91 | 202.51 | 82.78 | 100.71 |

LSMEAN= least squares mean
LSMEAN1=LSMEAN-test LSMEAN2=LSMEAN-ref.
RLSM12=T/R ratios (under non-fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

1. The mean plasma carbidopa levels for the test product and reference products reached maximum level of concentrations around 75.0-75.5 hours (Table #11 and Figures #9&10).

2. The 90% confidence intervals for the LSMEAN log-transformed

values for AUCt and Cmax were within the acceptable range of 80-125% (Table #13). The LSMEAN value for fluctuation of the test product was similar to the reference product fluctuation product value (Table #13).

There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCt and Cmax.

**Table #14**

**Mean Plasma Concentrations of Levodopa at Steady-State (Day-4) in 38 Subjects Following Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), every 8 hours for 10 doses (Unit: ng/mL)**

**(Test Lot #2C012B, Reference Lot #A6735)**

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| 0 | 0 | | 0 | | |
| 24 | 167.00 | 64.9 | 160 | 50.6 | 0.56 |
| 48 | 140.00 | 38.4 | 172 | 59.2 | 0.03 |
| 72 | 199.99 | 132.94 | 185.33 | 109.25 | 1.08 |
| 72.25 | 285.87 | 148.04 | 306.00 | 235.18 | 0.93 |
| 72.5 | 702.16 | 354.55 | 691.49 | 350.59 | 1.02 |
| 72.75 | 845.02 | 390.92 | 824.94 | 333.38 | 1.02 |
| 73 | 943.89 | 387.04 | 885.68 | 311.89 | 1.07 |
| 73.5 | 1034.34 | 361.06 | 1017.07 | 326.08 | 1.02 |
| 74 | 1103.02 | 321.36 | 984.57 | 278.04 | 1.12 |
| 74.5 | 1074.61 | 324.60 | 977.39 | 272.28 | 1.10 |
| 75 | 973.76 | 240.56 | 886.69 | 255.58 | 1.10 |
| 75.5 | 829.29 | 226.46 | 835.27 | 330.23 | 0.99 |
| 76 | 704.35 | 215.68 | 692.11 | 193.89 | 1.02 |
| 76.5 | 584.41 | 145.41 | 588.76 | 195.79 | 0.99 |
| 77 | 469.33 | 115.38 | 502.02 | 154.51 | 0.93 |
| 78 | 279.33 | 72.12 | 310.83 | 127.09 | 0.90 |
| 79 | 170.00 | 43.74 | 184.76 | 76.15 | 0.92 |
| 80 | 112.02 | 31.49 | 122.68 | 51.23 | 0.91 |

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

## Table #15
## Arithmetic Mean For Levodopa at Steady-State (Day-4) in 38 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), every 8 hours for 10 doses (Unit: ng/mL)

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCT | 4846.45 | 914.40 | 4735.28 | 882.40 | 1.02 |
| CAVG | 605.81 | 114.30 | 591.91 | 110.30 | 1.02 |
| CMAX | 1358.08 | 322.41 | 1308.56 | 328.09 | 1.04 |
| CMIN | 109.03 | 31.61 | 113.67 | 44.33 | 0.96 |
| FLUC1 | 2.06 | 0.34 | 2.02 | 0.39 | 1.02 |
| TMAX | 73.68 | 0.86 | 73.88 | 1.08 | 1.00 |

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
AUCT= $AUCT_{72-80}$
CAVG= AUCT/8
CMIN= Minimum measured plasma concentration over the final dosing interval.
FLUC1= [CMAX -CMIN]/CAVG

## Table #16
## LSMEANS AND 90% CONFIDENCE INTERVALS For Levodopa at Steady-State (Day-4) in 38 Subjects Following a Single Oral Dose of 1x(50mg/200mg Carbidopa/Levodopa ER tablet), every 8 hours for 10 doses (Unit: ng/mL)

| | LSM1 | LSM2 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|
| PARAMETER | | | | |
| LAUCT | 4760.76 | 4656.35 | 98.49 | 106.14 |
| LCAVG | 595.10 | 582.04 | 98.49 | 106.14 |
| LCMAX | 1319.03 | 1272.58 | 98.01 | 109.61 |

LSMEAN= least squares mean
LSMEAN1=LSMEAN-test LSMEAN2=LSMEAN-ref.
RLSM12=T/R ratios
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

1. The mean plasma levodopa levels for the test product and reference products reached maximum level of concentrations around 73.5-74.0 hours (Table #14 and Figures #11&12).

2. The 90% confidence intervals for the LSMEAN log-transformed

values for AUCt and Cmax were within the acceptable range of 80-125% (Table #16). The LSMEAN value for fluctuation of the test product was similar to the reference product fluctuation product value (Table #16).

There were no significant sequence, period or treatment effects (p less than 0.05) of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCt, AUCi and Cmax.

**VI. FORMULATION** (vol. #C1.14, p #6008)

Mylan's formulation for its Carbidopa and Levodopa ER Tablet 50 mg/200 mg is shown below:

| | Ingredient | mg per Tablet |
|---|---|---|
| 1 | Carbidopa, USP | [a]54.00 |
| 2 | Levodopa, USP | 200.00 |
| 3 | Cellulose | |
| 4 | Purified Water, USP | |
| 5 | Methylcellulose, USP<br>Premium) | |
| 6 | FD&C Blue | |
| 7 | FD&C Red | |
| 8 | Magnesium Stearate, | |

[a] Equivalent to 50.0 mg of Carbidopa, USP (anhydrous)

[b] The Purified Water, USP component is used as a processing aid and does not contribute to the total weight of the finished product. Therefore, quantities are expressed parenthetically.

**VIII. IN VITRO DISSOLUTION TESTING:** (vol. C1.2, pp #709-715)

The dissolution testing for the test and reference products are summarized below:

Method: USP 23 apparatus II (paddle) at 50 rpm
Medium: 900 mL of 0.1N HCl
Number of Tablets: 12

Test products: Mylan's Carbidopa/Levodopa ER Tablets, lot #2C012B

Reference products: Sinemet® CR Tablets, lot#A6735

The firm's specification to control the dissolution rate are as follows:

| Time (minutes) | %Released |
|---|---|
| 30 | |
| 60 | |
| 150 | |
| 240 | |

The dissolution testing results are presented in Table #17.

| **Table #17 In Vitro Dissolution Testing** |
|---|
| Drug (Generic Name): Carbidopa/Levodopa ER Tablet<br>Dose Strength: 50 mg/200 mg<br>ANDA No.: 75-091<br>Firm: Mylan Pharmaceuticals Inc.<br>Submission Date: March 13, 1997<br>File Name: 75091sd.397 |
| I. Conditions for Dissolution Testing: |

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of 0.1N HCl
Specifications:
Reference Drug: Sinemet CR
Assay Methodology

II. Results of In Vitro Dissolution Testing:

| Sampling Times (Minutes) | Test Product Carbidopa Lot #2C012B Whole Tablet Strength(mg) 50 | | | Reference Product Carbidopa Lot #A6735 Whole Tablet Strength(mg) 50 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 30 | 25 | | 15 | 39 | | 15 |
| 60 | 44 | | 16 | 61 | | 17 |
| 150 | 81 | | 11 | 88 | | 10 |
| 240 | 93 | | 6 | 90 | | 8 |

| Sampling Times (Minutes) | Test Product Levodopa Lot #2C012B Whole Tablet Strength(mg) 200 | | | Reference Product Levodopa Lot #A6735 Whole Tablet Strength(mg) 200 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 30 | 26 | | 15 | 39 | | 15 |
| 60 | 48 | | 15 | 61 | | 17 |
| 150 | 87 | | 9 | 88 | | 10 |
| 240 | 101 | | 4 | 90 | | 8 |

**VIII. COMMENTS:**

1. The firm's single-dose bioequivalence study #CBLV-9566 under fasting conditions, conducted on its 50 mg/200 mg Carbidopa-Levodopa ER tablet is acceptable. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax are within the acceptable range of 80-125% for Carbidopa and Levodopa.

2. The firm's single-dose bioequivalence study #CBLV-9567 under fasting and nonfasting conditions, conducted on its 50 mg/200 mg Carbidopa and Levodopa ER tablet is acceptable. The ratios of the test mean to the reference mean for AUCt, AUCi and Cmax are within the acceptable range of 0.80-1.25 for Carbidopa and

Levodopa under nonfasting conditions.

3. The firm's multiple-dose bioequivalence study #CBLV-9573, conducted on its 50 mg/200 mg Carbidopa and Levodopa ER tablet is acceptable. The 90% confidence intervals for the log-transformed AUC(72-80) and Cmax are within the acceptable range of 80-125% for Carbidopa and Levodopa.

**IX. DEFICIENCY COMMENTS:**

1. The firm is advised to submit complete dissolution profiles generated in different buffers media (such as citric acid or phosphate buffers), in the pH ranges: 1-1.5, 4-4.5, 6-6.5 and 7-7.5. The rotation basket (rpm) should be as follow: at 50 rpm and 75 rpm (paddle); and 100 rpm (basket). The sampling schedule as follow: 1, 2, 4 hours, and every two hours thereafter, until of the drug is released. The firm is advised to refer to the Division of Bioequivalence guidance 'Oral Extended (Control) Release Dosage Forms' dated September 09, 1993.

2. Since carbidopa and levodopa ER tablets are scored, therefore, dissolution profiles for half tablets are required in an addition to whole tablets.

3. The dissolution specifications for the test product will be established based on acceptable submitted dissolution data.

**X. RECOMMENDATIONS:**

1. The single-dose fasting bioequivalence study #CBLV-9566, conducted by Mylan Pharmaceuticals Inc., on its Carbidopa and Levodopa, 50 mg/200 mg extended release (ER) Tablet, lot #2C012B, comparing it to Sinemet® CR 50 mg/200 mg tablet, manufactured by Merck Sharp & Dohme, has been found incomplete by the Division of Bioequivalence. The firm should respond to the deficiency comments cited above.

2. The single-dose post-prandial bioequivalence study #CBLV-9567, conducted by Mylan Pharmaceuticals Inc., on its Carbidopa and Levodopa, 50 mg/200 mg extended release (ER) Tablet, lot #2C012B, comparing it to Sinemet® CR 50 mg/200 mg tablet, manufactured by Merck Sharp & Dohme, has been found incomplete by the Division of Bioequivalence. The firm should respond to

the deficiency comments cited above.

3. The multiple-dose steady-state bioequivalence study #CBLV-9573, conducted by Mylan Pharmaceuticals Inc., on its Carbidopa and Levodopa, 50 mg/200 mg extended release (ER) Tablet, lot #2C012B, comparing it to Sinemet® CR 50 mg/200 mg tablet, manufactured by Merck Sharp & Dohme, has been found incomplete by the Division of Bioequivalence. The firm should respond to the deficiency comments cited above.

The firm should be informed of the deficiency comments and recommendations.

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-091 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Carbidopa and Levodopa, 50 mg/200 mg ER Tablets

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. Please submit complete dissolution profiles data generated in different buffers media (such as citric acid or phosphate buffers), in the pH ranges: 1-1.5, 4-4.5, 6-6.5 and 7-7.5. The rotation basket (rpm) should be as follow: at 50 rpm and 75 rpm (paddle); and 100 rpm (basket). The sampling schedule as follow: 1, 2, 4 hours, and every two hours thereafter, until of the drug is released. You are advised to refer to the Division of Bioequivalence guidance 'Oral Extended (Control) Release Dosage Forms' dated September 09, 1993.

2. Since carbidopa and levodopa ER tablets are scored, therefore, dissolution profiles for half tablets are required in an addition to whole tablets.

3. The dissolution specifications for the test product will be established based on acceptable submitted dissolution data.

Sincerely yours,

Dale Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

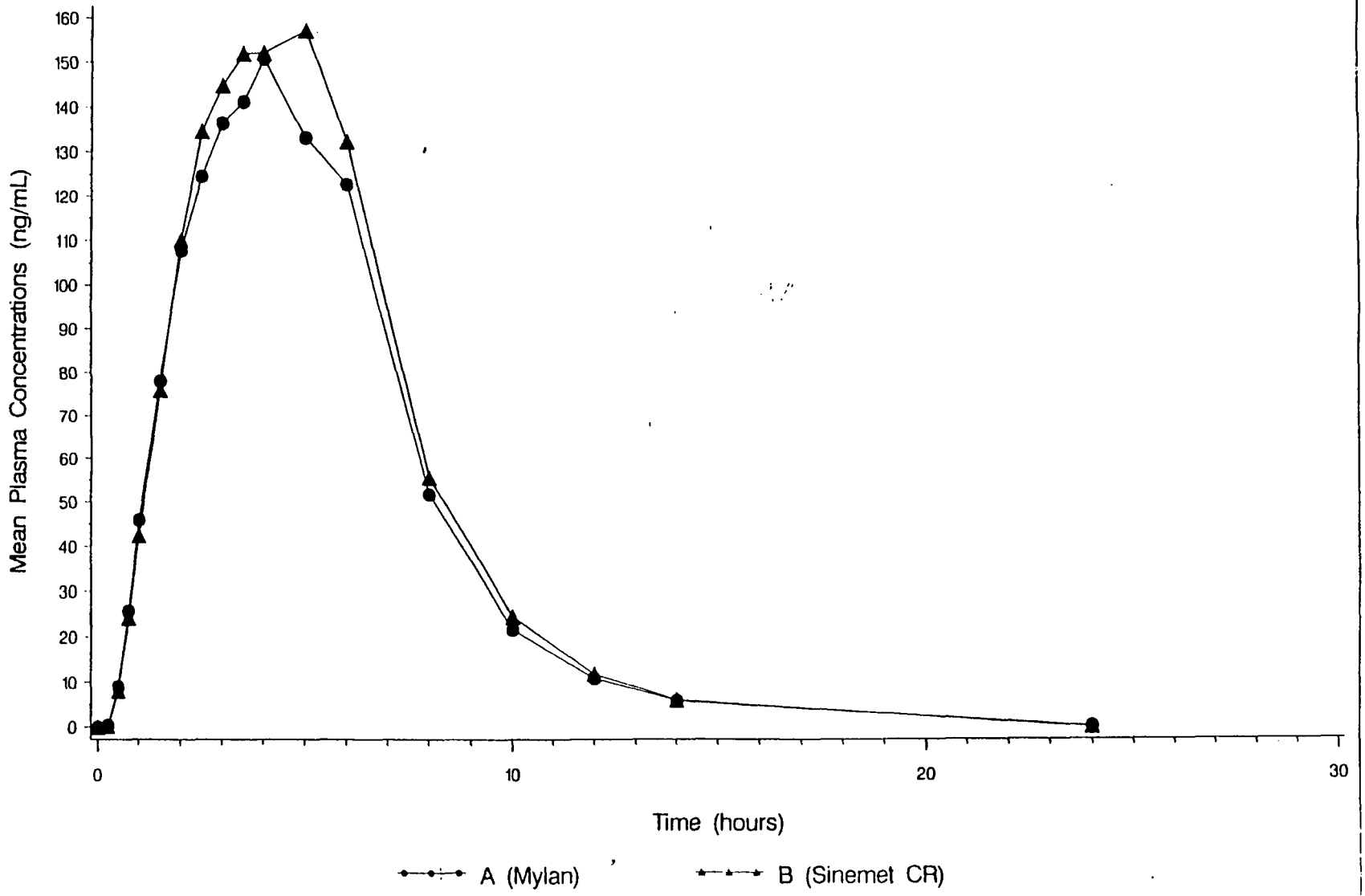
NDA # 75-091 Fig. #1

# CARBIDOPA/LEVODOPA (CBLV–9566)

## Total Dose: 50/200 (1x50/200 Tablet), Study Type: Fasting

## Mean Carbidopa Plasma Concentrations

## N= 44



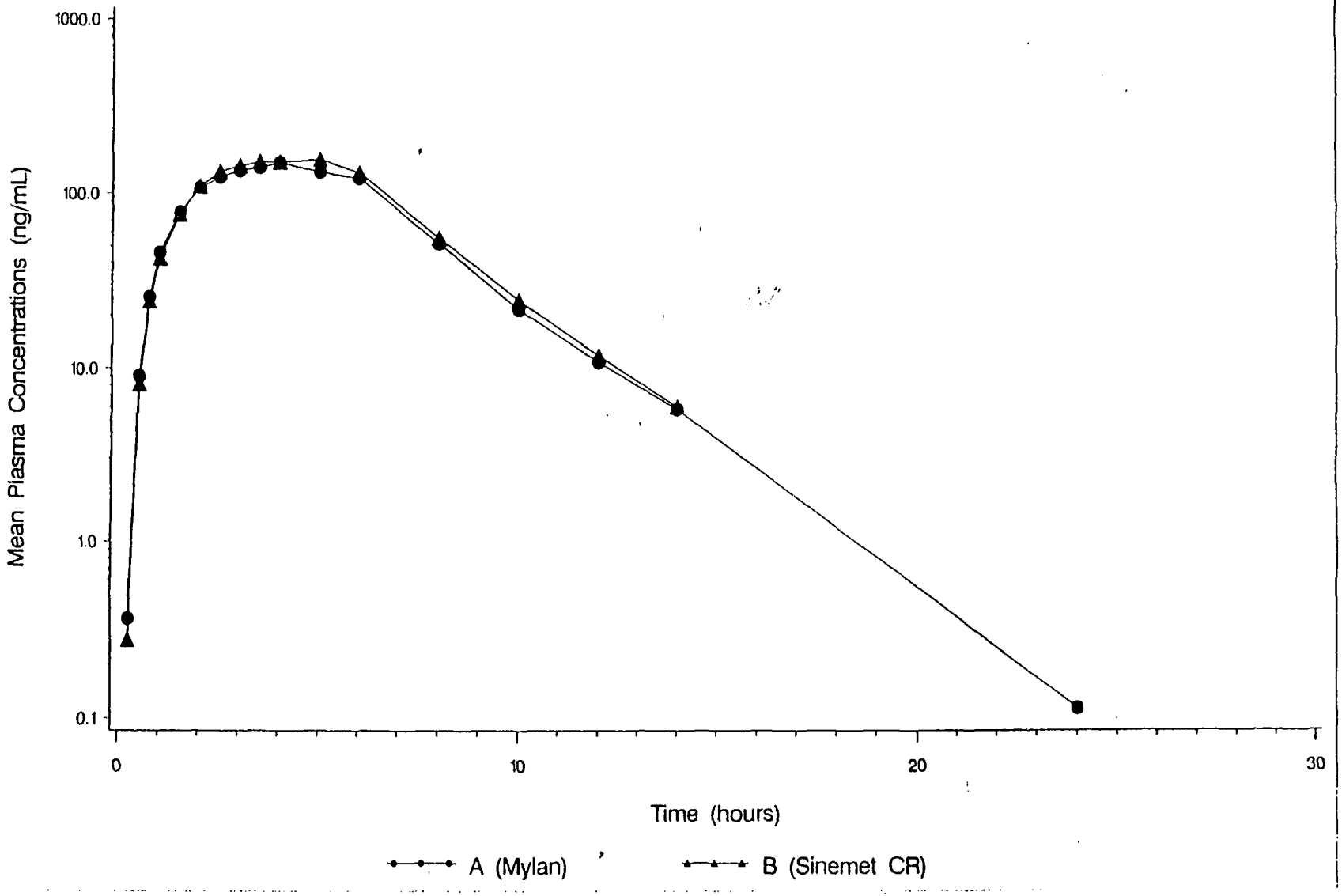
ANDA #75-091 Figure #2

# CARBIDOPA/LEVODOPA (CBLV–9566)

## Total Dose: 50/200 (1x50/200 Tablet), Study Type: Fasting

## Mean Carbidopa Plasma Concentrations

## N=44



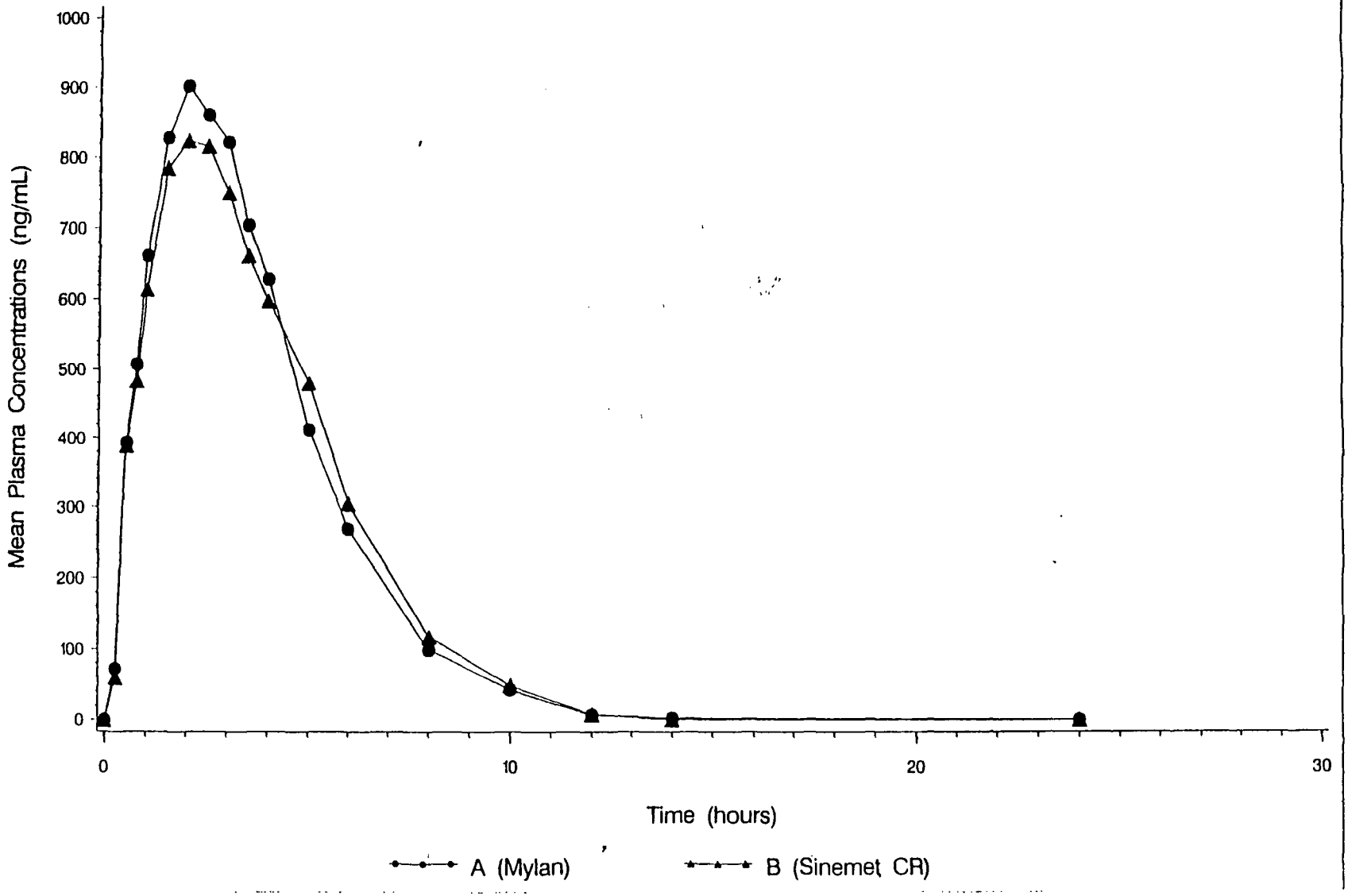
ANDA #75-091 F re #3

# CARBIDOPA/LEVODOPA (CBLV–9566)

## Total Dose: 50/200 (1x50/200 Tablet), Study Type: Fasting

## Mean Levodopa Plasma Concentrations

## N=44



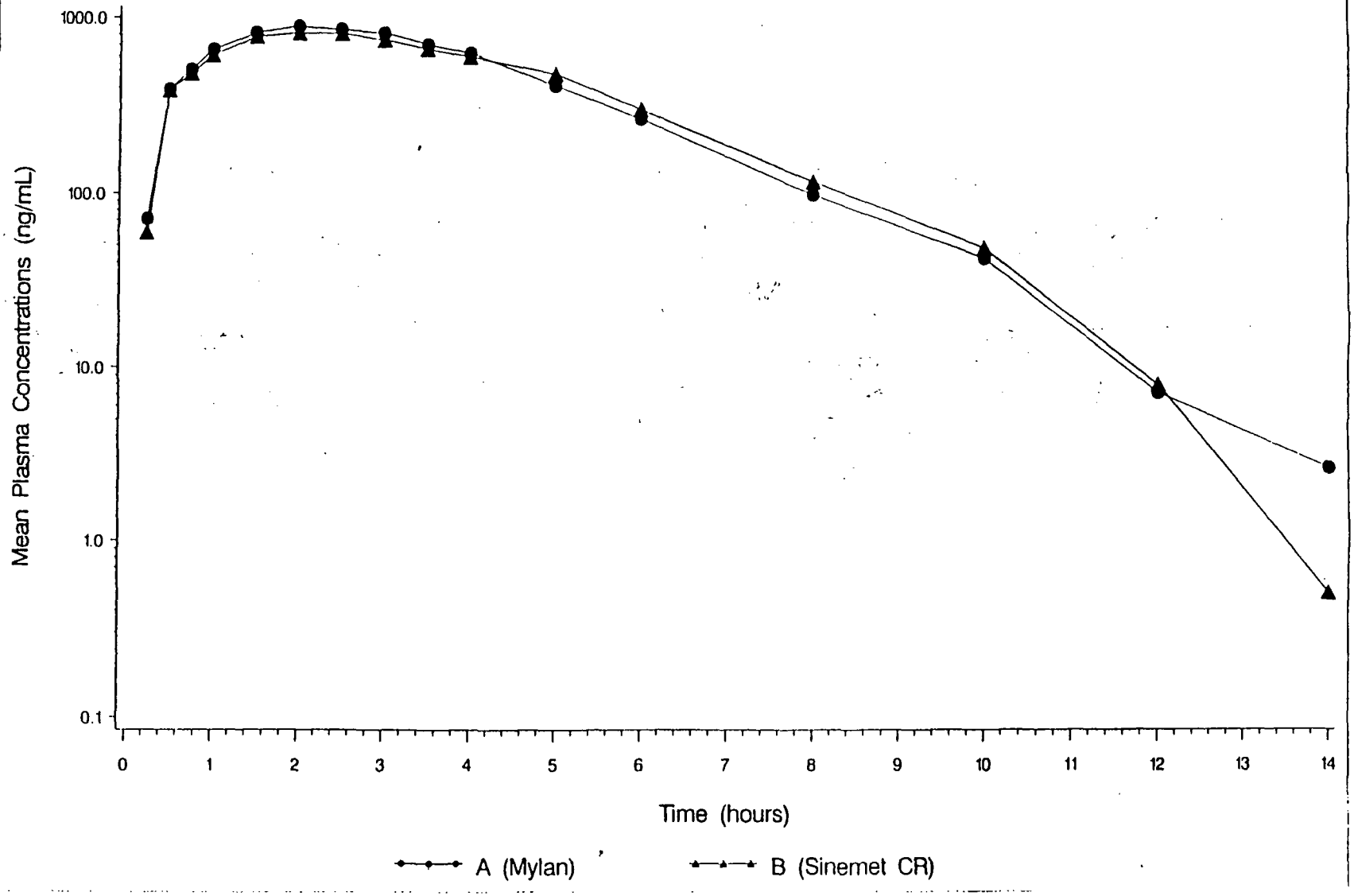
NDA #75-091 Figure #4

# CARBIDOPA/LEVODOPA (CBLV–9566)

Total Dose: 50/200 (1x50/200 Tablet), Study Type: Fasting

Mean Levodopa Plasma Concentrations

N=44



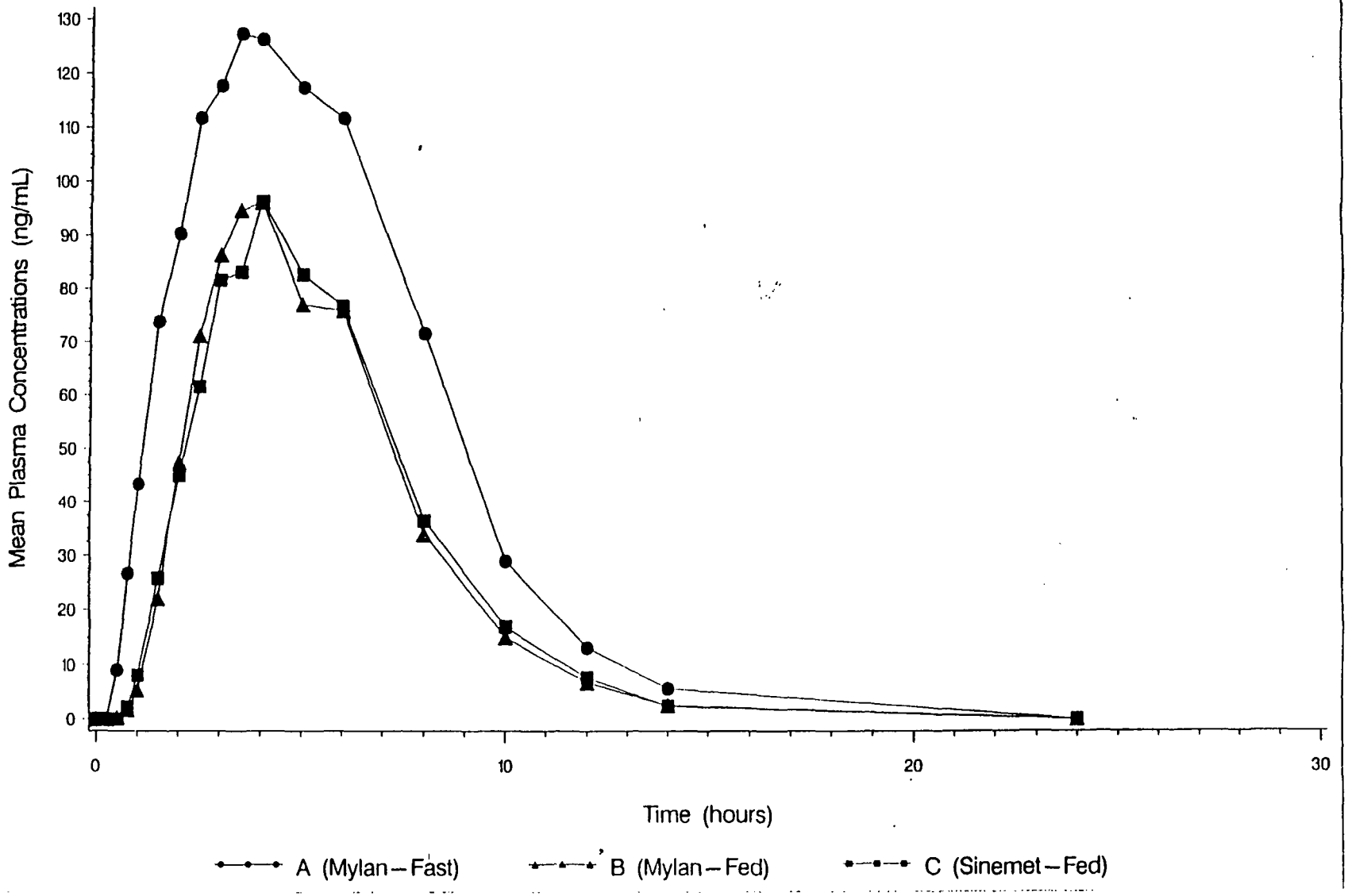
NDA # 75-091 Fig # 5

# CARBIDOPA/LEVODOPA (CBLV–9567)

## Total Dose: 50/200 (1x50/200 Tablet), Study Type: Fed

## Mean Carbidopa Plasma Concentrations

## N= 17



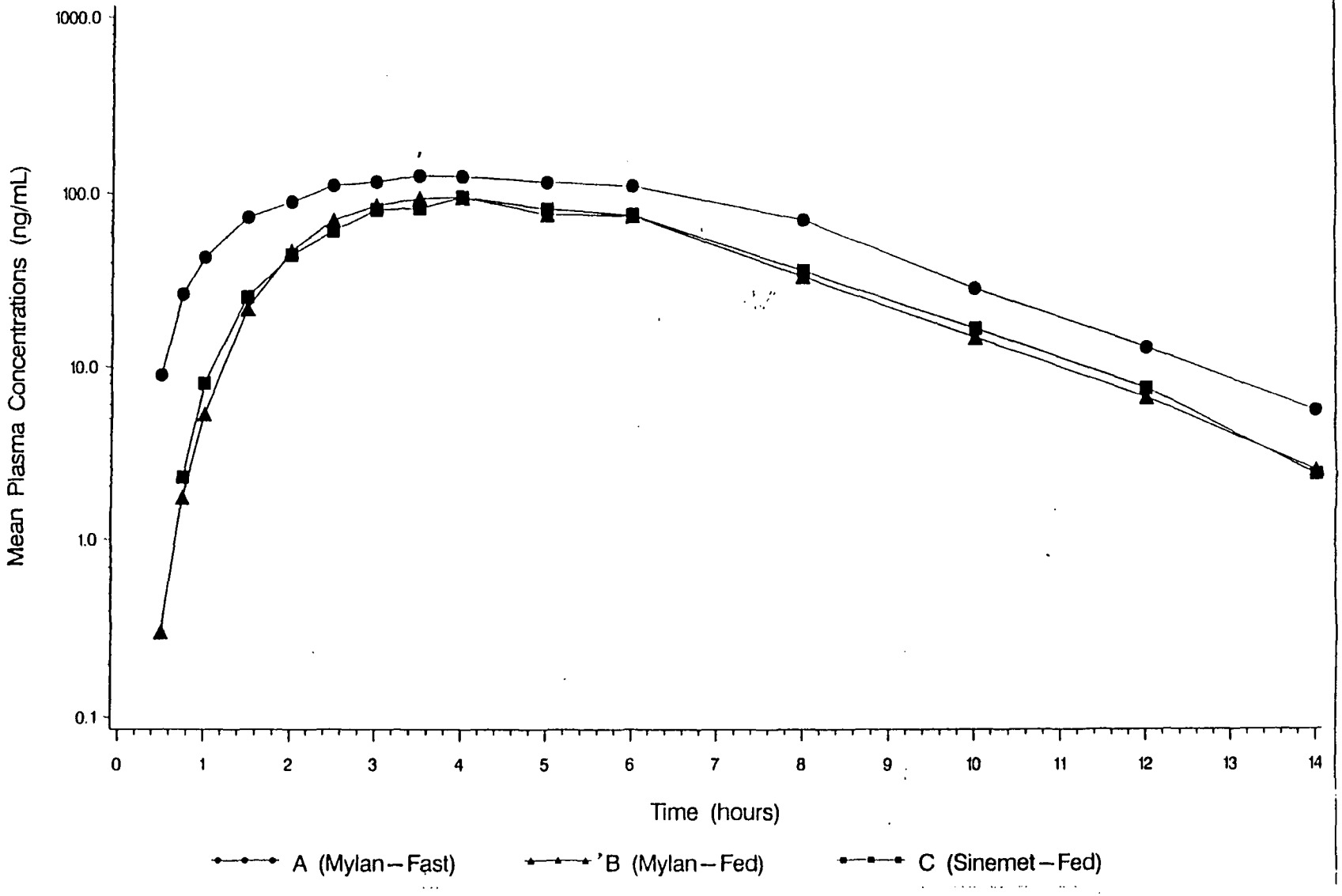
NDA #75-091 Fig #6

# CARBIDOPA/LEVODOPA (CBLV–9567)

Total Dose: 50/200 (1x50/200 Tablet), Study Type: Fed

Mean Carbidopa Plasma Concentrations

N= 17



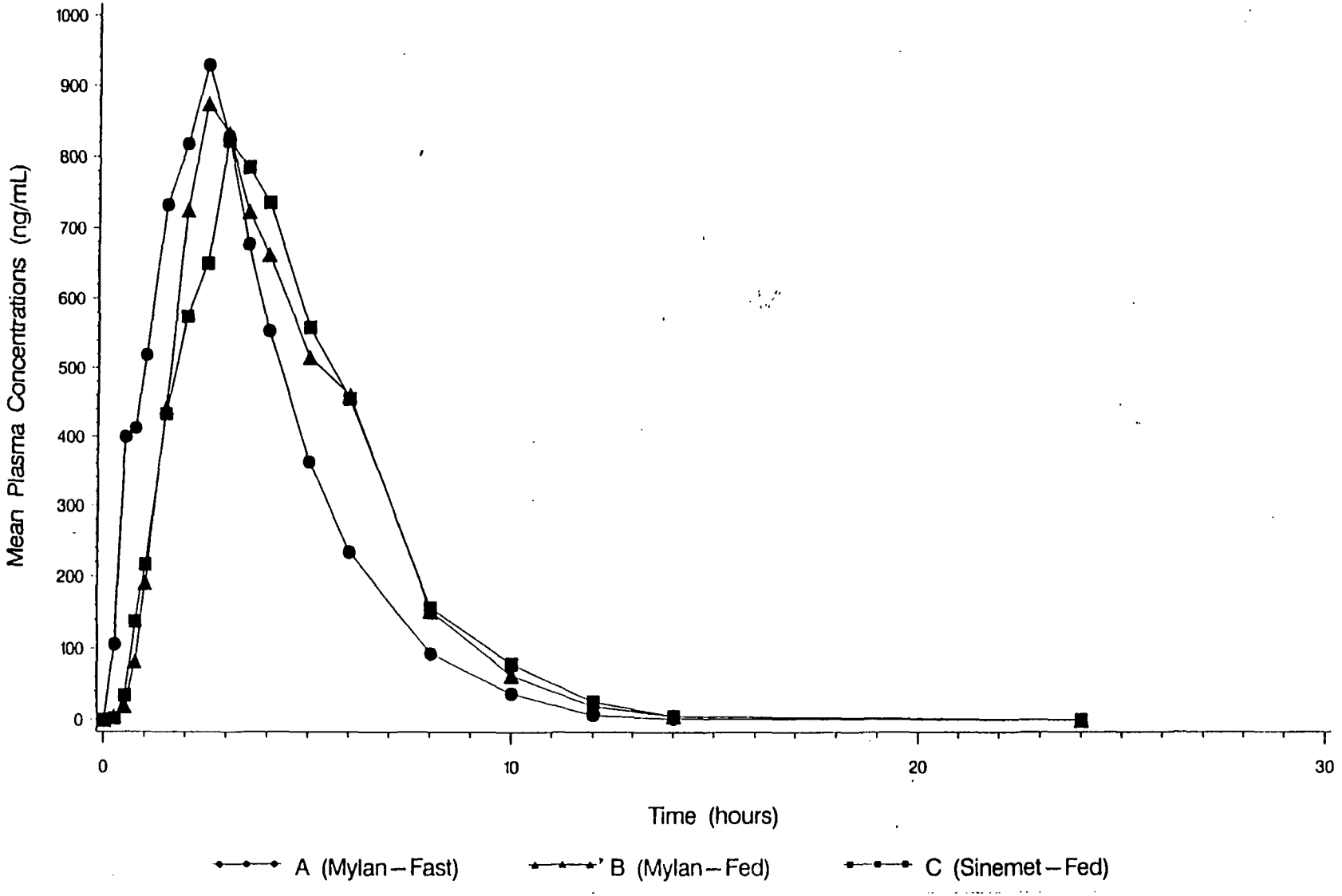
NDA #75-091 Figur F7

# CARBIDOPA/LEVODOPA (CBLV–9567)

## Total Dose: 50/200 (1x50/200 Tablet), Study Type: Fed

## Mean Levodopa Plasma Concentrations

## N= 17



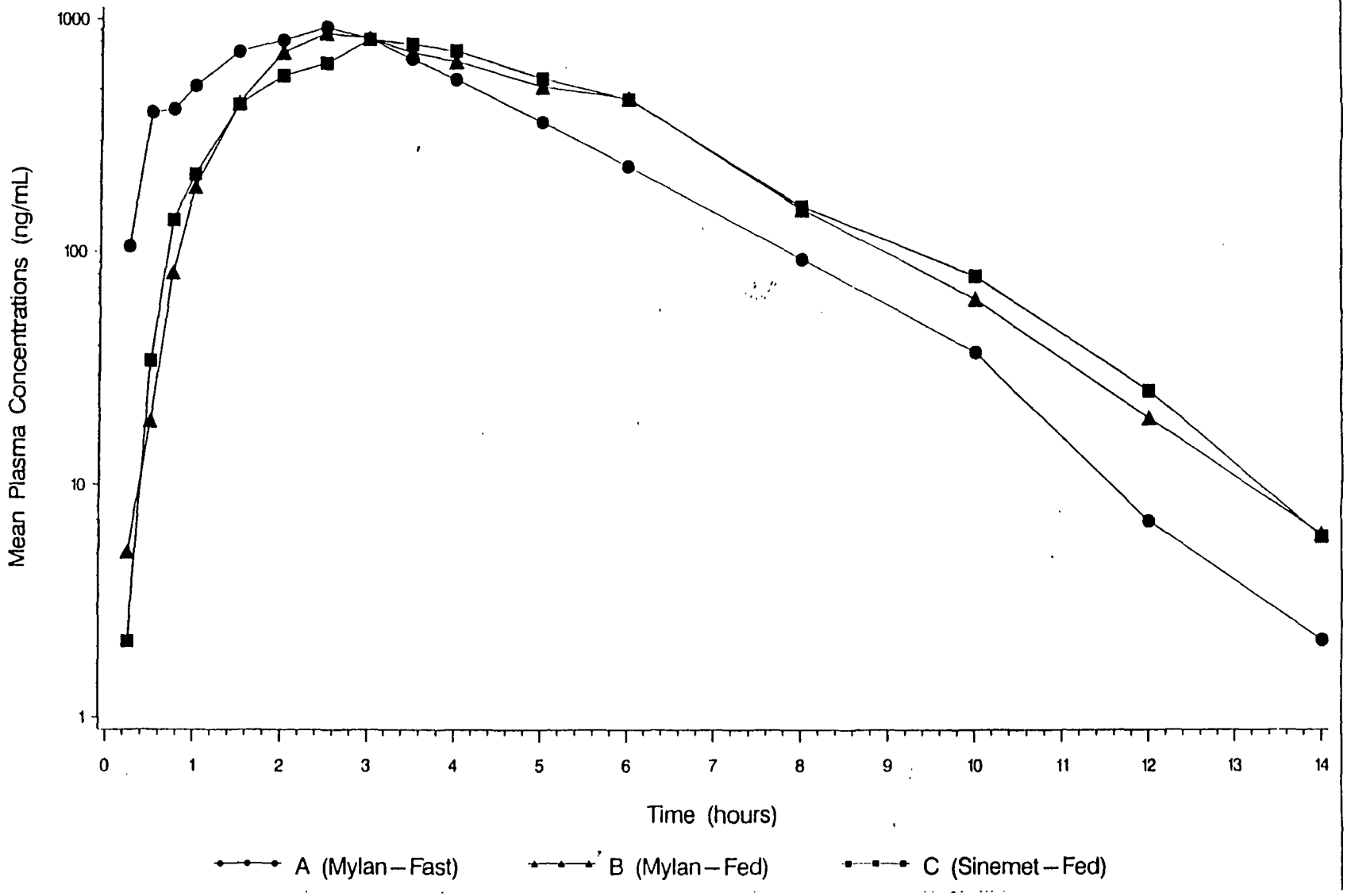
INDA #75-091 re #8

# CARBIDOPA/LEVODOPA (CBLV–9567)

Total Dose: 50/200 (1x50/200 Tablet), Study Type: Fed

Mean Levodopa Plasma Concentrations

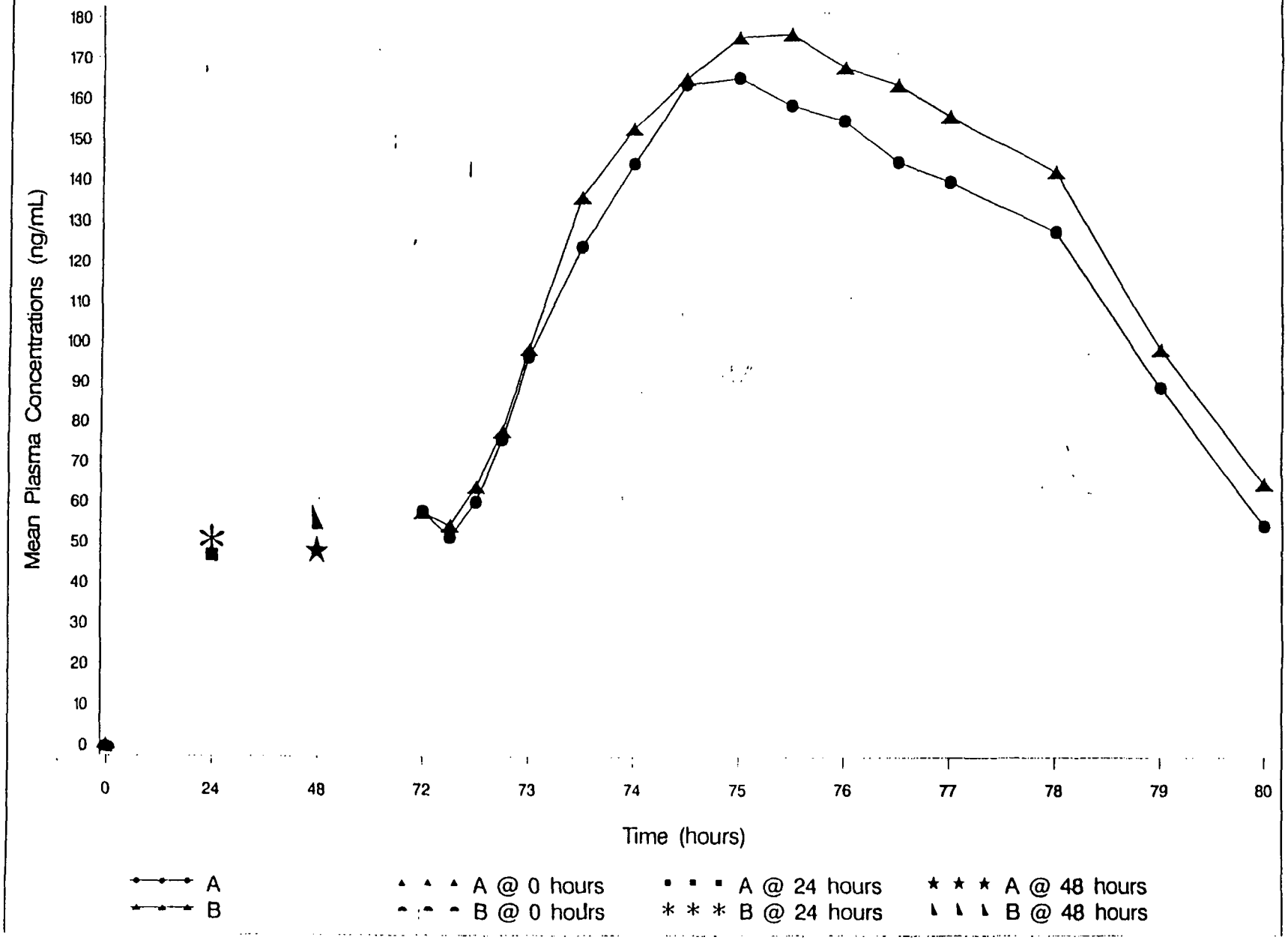
N= 17



NDA #75-091 Figure #9

# CARBIDOPA/LEVODOPA (CBLV–9573)

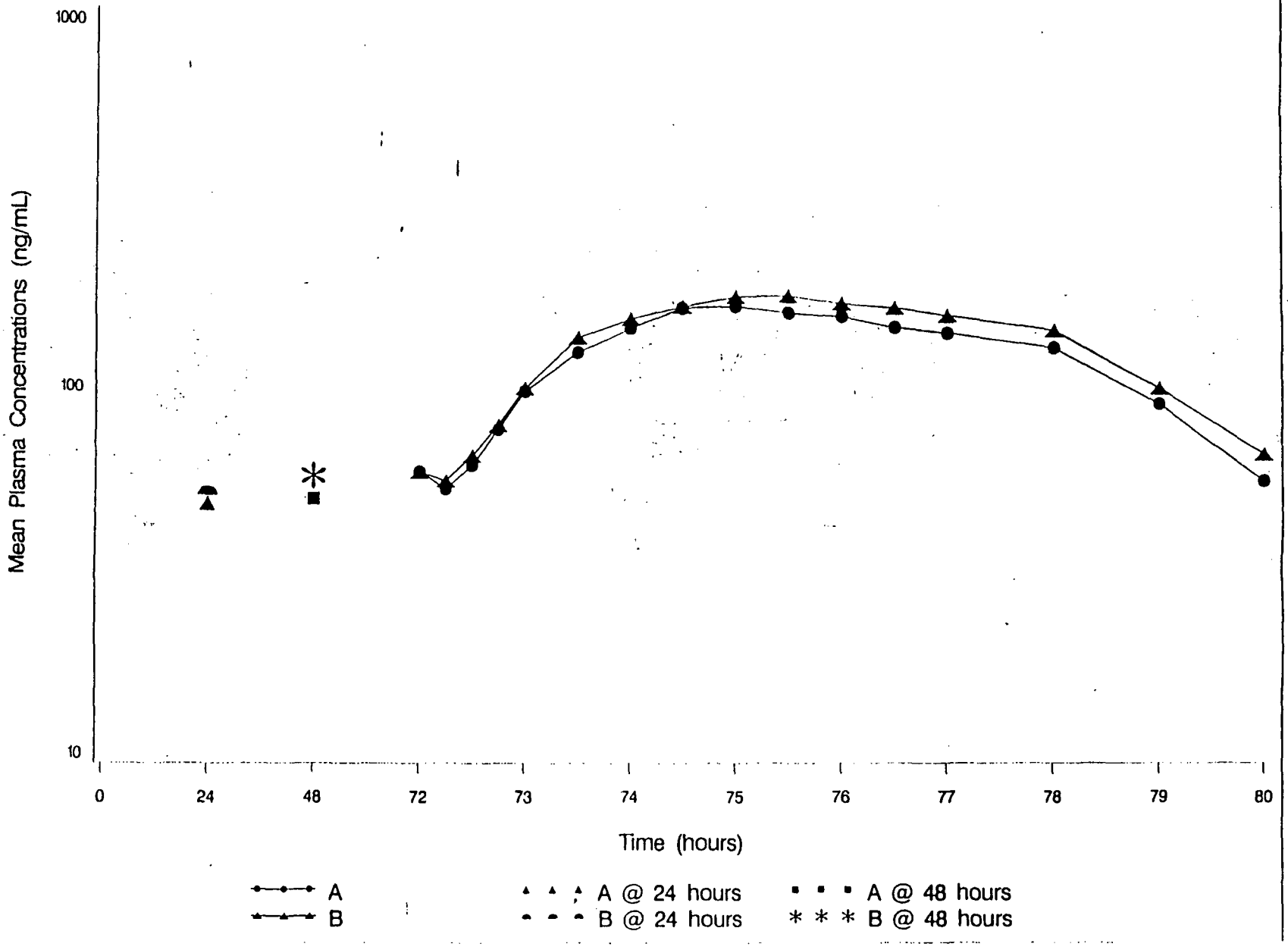
## Mean Carbidopa Plasma Concentrations



NDA #75-091 Figure #10

# CARBIDOPA/LEVODOPA (CBLV–9573)

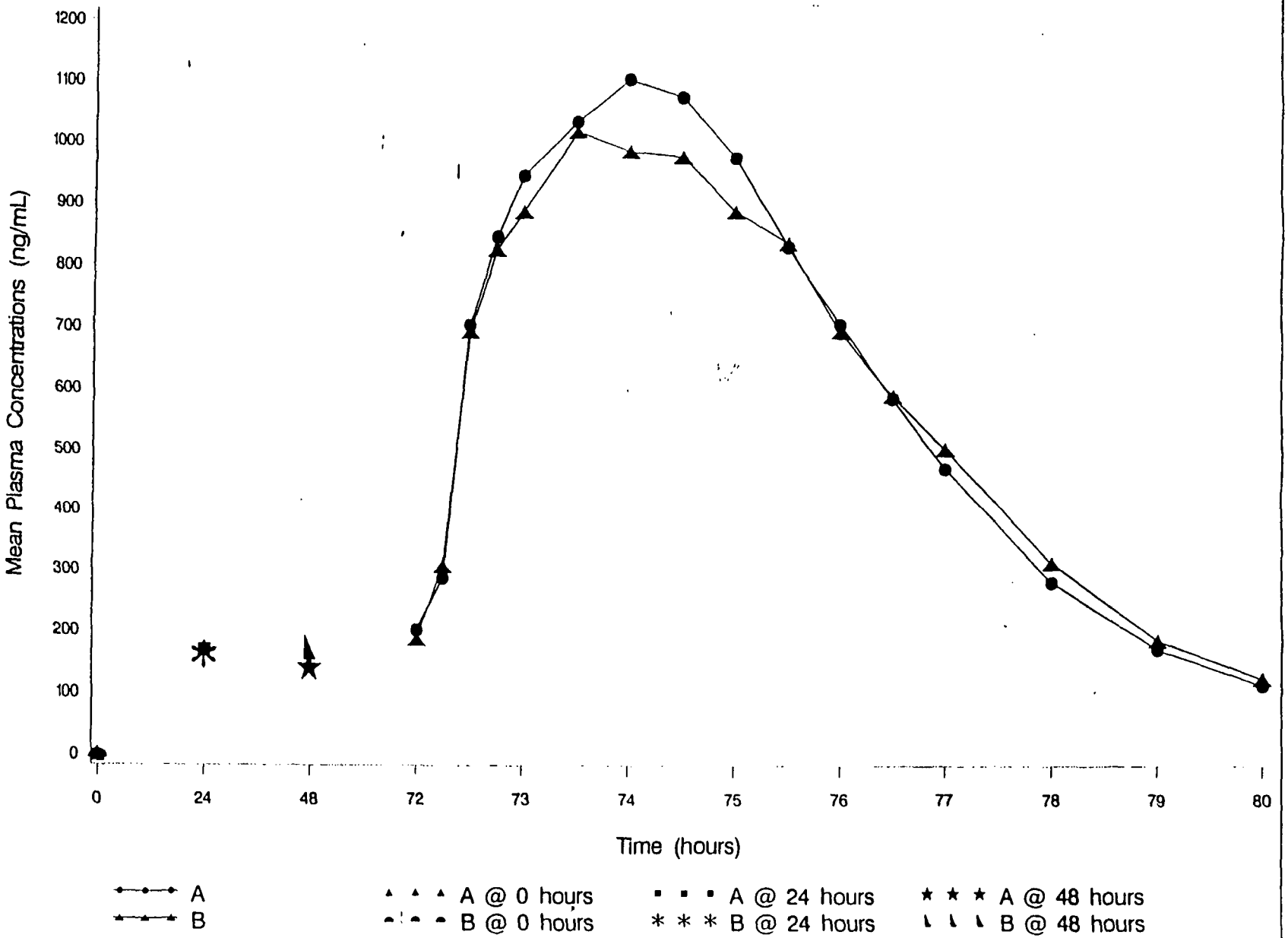
## Mean Carbidopa Plasma Concentrations



NDA #75-091 ure #11

# CARBIDOPA/LEVODOPA (CBLV–9573)

## Mean Levodopa Plasma Concentrations



ANDA #75-091 Figure #12

# CARBIDOPA/LEVODOPA (CBLV–9573)

## Mean Levodopa Plasma Concentrations