

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

74-937

APPLICATION NUMBER:

BIOEQUIVALENCE

JAN 28 1997

Ibuprofen Suspension, 100 mg/5 ml
ANDA # 74-937
Reviewer: Nhan L. Tran
WP #74937SD.796

The L. Perrigo Company
Allegan, Michigan
Submission Date:
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Review of Two Bioequivalence Studies

I. BACKGROUND INFORMATION:

Ibuprofen [2-(4-isobutylphenyl)propionic acid] is a nonsteroidal anti-inflammatory agent possessing analgesic and antipyretic activities. Ibuprofen is very slightly soluble in water (less than 1 mg/ml). The absorption from the gastrointestinal tract is rapid with peak plasma concentrations occurring at 1-2 hours. The compound is extensively metabolized to inactive metabolites with only 1 % or less being excreted unchanged. The plasma half-life of ibuprofen is approximately two hours. Ibuprofen is extensively bound to serum proteins (greater than 99%).

II. OBJECTIVE:

To compare the bioavailability/bioequivalence of the test and reference products under fasting and fed conditions. A two-way crossover study under fasting conditions and a three-way crossover study under fed conditions were performed to compare the bioequivalence of ibuprofen suspension, 100 mg/5 ml produced by The L. Perrigo Company, to the corresponding 100 mg/5 ml Children's Motrin Ibuprofen Oral Suspension reference product produced by McNeil Consumer Products Company.

III. REVIEW OF THE FASTING AND FED STUDIES:

The bioequivalence studies were performed by PharmaKinetics, Baltimore, Maryland, under the direction of C. Ferguson, M.D., Principal Investigator. The products were administered orally to healthy subjects between the ages of 18 and 45, weighing within +/- 15% of their ideal body weight according to Metropolitan Life Insurance Company Bulletin, 1983. All subjects were assessed to be normal by physical examination, blood chemistry, urinalysis, and hematological evaluation. The subjects were prohibited from (1) using any drugs during the two week period prior to the start of study, (2) taking any concurrent

medication during the study period, (3) consuming alcohol within 48 hours prior to dosing, (4) consuming caffeine within three days prior to dosing. The subjects were housed in the clinic the evening prior to each drug administration and for each entire 12-hour study period. In the fasting studies the subjects fasted from 10 hours before until four hours following drug administration. At four and nine hours after dosing, standardized meals were given to the subjects. All meals were kept identical throughout each study phase.

In the fed study, the high-fat meal consumed by each subject 15 min prior to dosing consisted of 1 fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, 1 buttered English muffin, 1 serving of hash brown potatoes, 6 oz of orange juice, and 8 oz. of whole milk. Each subject signed a written informed consent. The study was approved by the Internal Review Board of PharmaKinetics. All washout periods were one week.

The products used in the bioequivalence studies were:

Test: Ibuprofen, 200 mg (10ml), Lot # 5ZA02V, expiration date of 05/97.

Potency: 95% - 99% and batch size:

Reference: Children's Motrin[®], 200mg (10ml), McNeil Consumer Products Co., Lot # PLM827, expiration date of 09/97. Potency: 97% - 98%

Ibuprofen concentration of the test product is within 5% of the ibuprofen concentration of the reference product.

All doses were administered with 240 ml of water.

Blood samples (10 ml) were obtained from an antecubital vein using 10 ml Vacutainers[®] at 0, 0.16, 0.33, 0.5, 0.66, 0.83, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10 and 12 hours post-dose. The samples were centrifuged, and the plasma was stored frozen at -20°C until assay.

Analytical Methodology:

The analyses were performed by PharmaKinetics. Plasma spiked with internal

Data Analysis:

All ANOVA's were performed with SAS. For all analyses, effects were considered statistically significant if the probability associated with F was less than 0.05. The 90% confidence levels were calculated using one-sided t-tests.

RESULTS

1. Assay Method Validation (NOT TO BE RELEASED UNDER FOI)

Method Development: The contract laboratory developed a simple method for the quantification of ibuprofen in plasma samples.

1

Pre-study Validation:

Specificity: submitted did not show interference at the retention time of either drug peak or internal standard peak. Thus the specificity of the assay was demonstrated.

Sensitivity: The Sponsor indicated that the sensitivity of the method was 1.0 µg/ml. At this concentration, the %CV was 12.2% and accuracy was 105%.

Recovery: Percent recovery was determined by comparing the peak of ibuprofen from serum sample extracted according to the method analysis to the absolute peak height of an equivalent standard in methanol. Results are shown below:

Conc. (µg/ml)	1.0	10.0	50.0	4.0 (In.St)
% Recovery	86.4	86.7	93.9	78.7
%CV	4.63	6.33	9.10	14.0
N	7	7	7	7

Linearity: The firm reported that the standard curves were linear from 1.0 µg/ml to 100 µg/ml with 1/concentration as weighting factor. The R value was greater than 0.997.

Accuracy: Intra day accuracy was 89% to 114% for ibuprofen at 50 µg/ml, 10 µg/ml, and 1 µg/ml. The inter day accuracy was 98.8% µg/ml to 102.0 µg/ml for the same concentrations.

Precision: At the concentration 50 µg/ml, 10 µg/ml, and 1 µg/ml, the intra and inter day precision were 2.32% to 12.2% and 1.24% to 12.9% respectively.

Stability: The stability of ibuprofen after four freeze-thaw cycles for concentrations 50 µg/ml and 1 µg/ml was demonstrated. The mean % found was 94.6% and 115% respectively. At room temperature for 24 hours, the mean %

found was 105% and 101% for concentration 50 $\mu\text{g/ml}$ and 1 $\mu\text{g/ml}$ respectively. Autosampler stability was shown by injecting the control samples after a period of 40 hours at room temperature. The mean % found was 100%, 101% and 107% for concentrations 30 $\mu\text{g/ml}$, 10 $\mu\text{g/ml}$, and 2 $\mu\text{g/ml}$ respectively.

During Study Validation: The during study validation was performed for ibuprofen. For all runs, the R values for all standard curves were greater than 0.995 for ibuprofen with 1/concentration as weighting factor. Thus the linearity was documented.

The accuracy and precision for during study were between 98.3% to 105% and 1.56% to 5.89% respectively for control and standard samples.

Long term stability was performed by the Sponsor. Serum samples (for stability testing) spiked with known concentration of ibuprofen were prepared on April 26, 1996 and stored with the study samples at -20°C until assay in May 1996. The percent change of the stability samples (75 mcg/ml and 2.5 mcg/ml) after one month storage was about 3% for 75 mcg/ml sample and 22% for 2.5 mcg/ml samples. The firm indicated that the results for 2.5 mcg/ml was higher than the theoretical values probably due to dilution error. The firm repeated the 2.5 mcg/ml samples and found that the percent difference about 6%. Thus the long term stability of the samples was demonstrated.

From bioequivalence point of view, the assay is validated and no interferences from endogenous plasma components or other sources were observed. Stability studies reveal no problem with ibuprofen stored in plasma over the period of the study. There was no mention of the presence or absence of assay interference by metabolites. Validation data is therefore acceptable.

2. PHARMACOKINETICS AND STATISTICAL ANALYSES

A. FASTING STUDY

Of 26 subjects enrolled in the study, 25 completed. Only one subject (#4) did not return for personal reason for phase II dosing. Samples from this subject were not assayed.

Six of the subjects experienced a total of 7 mild to moderate adverse events during the study as follows: For test product: subject #8 (lightheaded), #15 (weakness), #17 (lightheaded), #22 (nausea) and for the reference product: subject #2 (increased diastolic), #12 (diarrhea), #22 (stomach ache), but overall, the drug products were well tolerated by all the subjects.

The mean plasma concentrations at each time point for the test and reference products are shown in table below:

Time (hrs)	Concentration (mcg/ml)	
	Test (SD)	Reference (SD)
0	0.0	0.0
0.167	8.32 (5.33)	9.46 (6.42)
0.333	18.07 (8.46)	19.85 (6.62)
0.5	22.83 (6.73)	23.56 (6.27)
0.667	22.87 (6.00)	23.78 (4.51)
0.833	21.93 (4.70)	22.41 (3.78)
1	20.96 (4.46)	20.77 (3.34)
1.33	18.64 (2.58)	18.33 (2.93)
1.667	17.00 (3.61)	16.36 (2.99)
2	14.97 (3.12)	14.53 (2.93)
2.5	12.66 (3.01)	12.25 (2.79)
3	10.86 (3.11)	10.52 (2.88)
4	8.10 (2.70)	7.56 (2.18)
5	6.06 (2.23)	5.63 (1.71)
6	3.84 (1.69)	3.57 (1.28)
8	1.90 (1.17)	1.66 (1.04)
10	0.79 (0.91)	0.71 (0.79)
12	0.26 (0.55)	0.10 (0.36)

The means AUC(0-t), AUC(0-inf), Cmax, Tmax, T1/2 and Kel are presented in table below.

Parameter	Test (%CV) (N=25)	Reference (%CV) (N=25)	Test/Ref
.AUC(0-t)	77.94 (24.7%)	75.30 (23.4%)	1.04
AUC(0-∞)	82.01 (24.2)	79.62 (22.4)	1.03
..Cmax	25.53 (20.5)	25.94 (18.5)	0.98
...Tmax	0.72 (49.9)	0.57 (38.0)	1.27
T1/2	2.03 (19.0)	2.01 (16.3)	1.01
Kel	0.35 (17.7)	0.35 (15.5)	1.00

*: Unit of AUC in mcg/ml x hr, **: unit of Cmax in mcg/ml and ***: unit of time in hour.

ANOVA comparisons of the pharmacokinetic parameters revealed no statistical differences between the test and reference formulations for mean AUC(0-t), AUC(0-inf), and Cmax. The 90% confidence intervals (log transformed) are shown below:

Parameter			90% C.I.Limits
LAUC(0-t)	4.32	4.29	98% - 108%
LAUC(0-∞)	4.38	4.35	98% - 108%
LCmax	3.22	3.24	92% - 103%

Data was verified including ANOVA and no discrepancies in the data reported were found.

B. NON FASTING STUDY

18 subjects were enrolled in this study. They were given a single dose of 200 mg on three occasions separated by one week. The test and reference drug lots were identical to the ones used in the fasting study.

All subjects completed the study and two of the subjects experienced an adverse event during the study: Subject #4 and #10 experienced increased diastolic blood pressure and both were on the test drug. When all subjects' samples were analyzed, of 18 subjects completing the study, one subject (#10) was eliminated due to the interference at the drug peak. This subject admitted to taking acetaminophen during the course of the study.

The mean plasma concentrations at each time point for the test and reference products are presented below:

Mean Concentration (mcg/ml), N=17			
Time (hrs)	Test-Fast (SD)	Ref.-Fed (SD)	Test-Fed (SD)
0	0.0	0.0	0.00
0.167	5.22 (3.06)	2.80 (3.21)	1.29 (1.93)
0.333	14.61 (5.98)	7.77 (4.64)	4.50 (2.44)
0.5	18.35 (8.00)	10.26 (4.49)	6.91 (2.73)
0.667	18.45 (5.20)	9.62 (3.46)	8.02 (2.53)
0.833	17.51 (4.15)	9.65 (2.98)	8.61 (2.32)
1	17.13 (4.12)	9.61 (2.81)	9.17 (2.07)
1.33	15.21 (3.84)	8.98 (2.15)	9.33 (1.89)
1.667	13.63 (3.17)	9.03 (2.16)	9.53 (1.78)
2	11.89 (2.48)	8.80 (1.66)	9.46 (1.94)
2.5	9.74 (1.71)	8.54 (1.30)	9.39 (1.82)
3	8.22 (1.37)	8.24 (2.01)	9.25 (2.01)
4	6.22 (1.18)	7.59 (2.00)	9.11 (1.98)
5	4.86 (2.05)	5.96 (1.89)	6.72 (1.54)
6	3.09 (1.21)	4.06 (1.54)	4.53 (1.16)
8	1.47 (0.74)	1.97 (0.92)	2.12 (0.59)
10	0.44 (0.63)	0.89 (0.76)	1.02 (0.61)
12	0.00 (0.00)	0.07 (0.30)	0.00 (0.00)

Means Pharmacokinetic Parameters

	T-Fed(CV) (N=17)	R-Fed (CV) (N=17)	T-Fast (CV) (N=17)	T/R (Fed/Fed)
.AUC(0-t)	56.57 (14.60)	53.38 (17.78)	60.42 (14.89)	1.06
AUC(0-∞)	60.53 (14.19)	57.32 (17.09)	64.28 (13.95)	1.06
..Cmax	11.33 (10.09)	12.33 (28.18)	22.03 (21.71)	0.92
...Tmax	2.22 (55.32)	1.09 (81.84)	0.95 (115.08)	2.05
T1/2	1.99 (11.95)	2.02 (14.22)	1.98 (12.85)	0.99
Kel	0.35 (12.44)	0.35 (13.50)	0.36 (12.80)	1.01

*: Unit of AUC in mcg/ml x hr, **: unit of Cmax in mcg/ml and ***: unit of time in hour.

The ratio of the least squares means (Log transformed) is shown below:

Parameter	Test (Fed)/Reference (Fed)
AUC(0-t)	1.07
AUC(0-∞)	1.06
Cmax	0.94

The relative bioavailabilities were 107% for AUC(0-t) and 106% for AUC(0-infinity) and 94% for Cmax.

Although the means AUC for all treatments were comparable, the Cmax of the test under fasting conditions (22.03 mcg/ml) was higher than that of the test product under fed (11.33 mcg/ml) and the reference product (12.33 mcg/ml) under fed conditions. Tmax for the test formulation under fasting conditions (Tmax=0.95 hours) was found to be lower than test product under fed conditions (Tmax=2.23 hours).

IV. FORMULATION

Components	mg/5ml
1. Ibuprofen	100
2. Corn Syrup	
3. Sorbitol	
4. Glycerin	
5. _____ 1 Methylcellulose	
6. Propylene Glycol	
7. Xanthan Gum	
8. Citric Acid,	
9. Butylparaben	
10. Sodium Benzoate	
11. D&C Red #33	
12. FD&C Red #40	
13. FD&C Yellow #6	
14. Flavor	
15. Purified Water	
Total	100

V. IN-VITRO DISSOLUTION

Ibuprofen oral suspension dissolution study was conducted by the Sponsor using the USP Method and Conditions for ibuprofen Oral Suspension (USP 23, Third Supplement, page 2941) as follows:

USP Apparatus II, 50 RPM in 900 ml of 0.05M Phosphate buffer, pH 7.2, at 37°C
Specification: NLT (Q) = 80% of the labeled amount of ibuprofen is dissolved in 60 minutes.

In Vitro Dissolution Testing

Drug: Ibuprofen Oral Suspension
Dose Strength: 100 mg/5ml
ANDA No.: 74-937
Firm: L. Perrigo Company
Submission Date: July 26, 1996
File Name: 74937SD.796

I. Conditions for Dissolution Testing: USP Method.

USP XXII, Paddle, Speed: 50 RPM, No. Units Tested: 12
 Medium: 0.05M Phosphate buffer, pH 7.2, Volume: 900 ml.
 Specifications: NLT (Q) =
 Reference Drug: Children's Motrin Ibuprofen Oral Suspension 100mg/5ml
 Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #: 5ZA02V Strength(mg): 100 mg/5ml			Reference Product Lot # : PLM827 Strength(mg): 100mg/5ml		
	Mean %	Range	%CV	Mean %	Range	%CV
15	101.2		0.6	100.1		0.9
30	101.5		1.0	100.2		0.8
45	101.7		0.7	100.2		0.8
60	101.6		1.0	99.6		1.4

VI. RECOMMENDATIONS

1. The fasting bioequivalence study conducted by L Perrigo Company on its ibuprofen oral suspension 100 mg/5ml, lot # 5ZA02V, comparing it to Children's Motrin[®] Ibuprofen Oral Suspension 100 mg/5ml, lot # PLM827 produced by McNeil Consumer Products has been found acceptable by the Division of Bioequivalence. The study results demonstrate that Perrigo's ibuprofen oral suspension 100mg/5ml is bioequivalent to the reference product, Children's Motrin[®] Ibuprofen Oral Suspension 100 mg/5ml produced by McNeil Consumer Products under fasting conditions.

2. The non-fasting bioequivalence study conducted by L Perrigo Company on its ibuprofen oral suspension 100 mg/5ml, lot # 5ZA02V, comparing it to Children's Motrin[®] Ibuprofen Oral Suspension 100 mg/5ml, lot # PLM827 produced by McNeil Consumer Products has been found acceptable by the Division of Bioequivalence. The study results demonstrate that Perrigo's ibuprofen oral suspension 100mg/5ml is bioequivalent to the reference product, Children's Motrin[®] Ibuprofen Oral Suspension 100 mg/5ml produced by McNeil Consumer Products under non-fasting conditions.

3. The dissolution study conducted by L Perrigo Company on its ibuprofen oral suspension 100 mg/5ml, lot # 5ZA02V, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The testing should be conducted on 12 individual dosage units each of the test and reference product employing 900 ml of phosphate buffer, pH 7.2, at 37°C using USP XXII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

Not less than _____ of the labeled amount of the drug
in the dosage form is dissolved in _____ minutes.

4. From the Bioequivalence point of view the firm has met the requirements of in-vivo bioequivalency and in-vivo dissolution testing, and the application is acceptable.

Nhan L. Tran, Ph.D
Division of Bioequivalence., RB II.

Nhan L. Tran Jan 21, 97

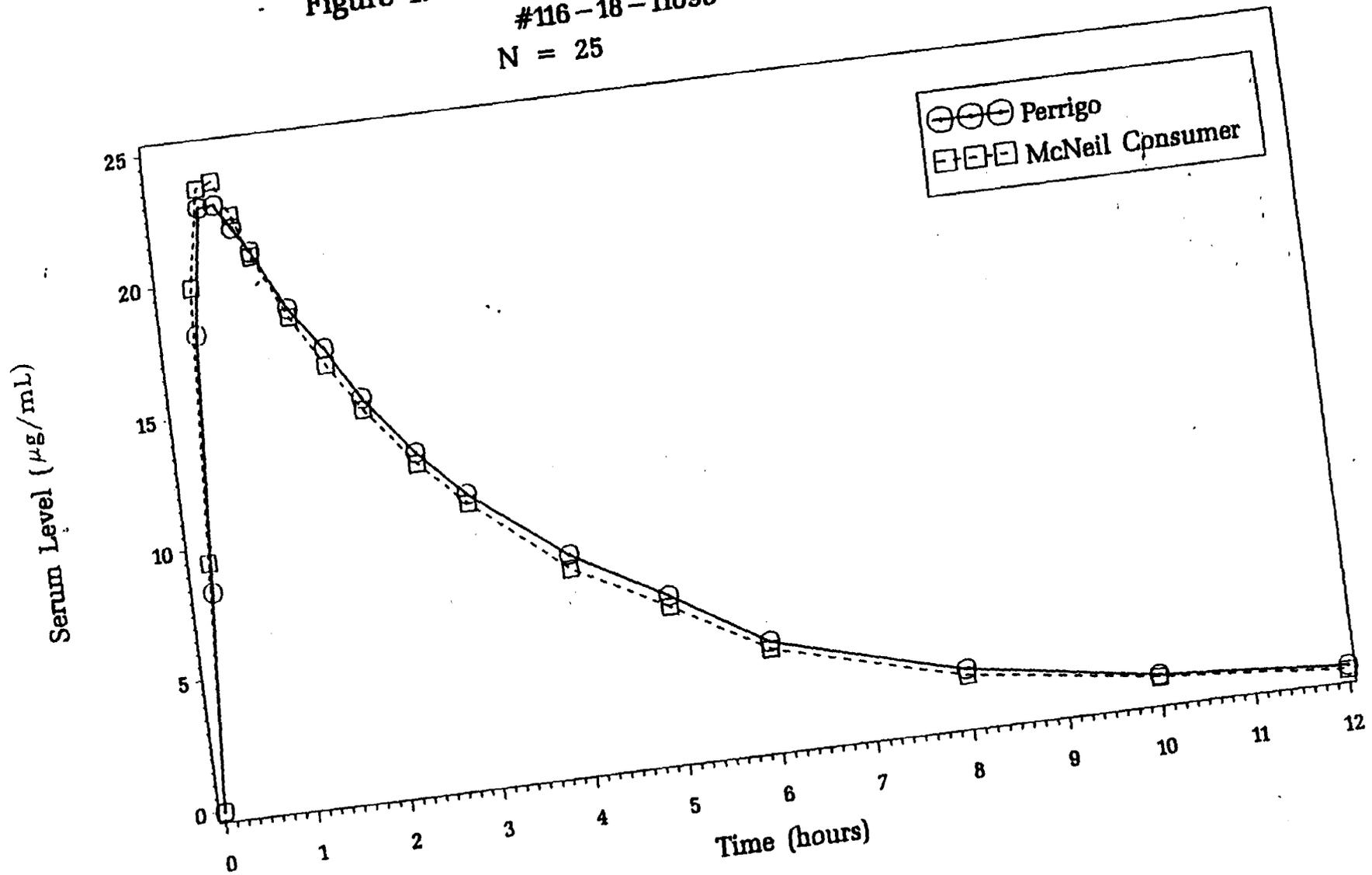
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Concur: *Rabindra Patnaik* Date: 1/28/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

Figure 1: Mean Naprofen Serum Levels
#116-18-11096

N = 25



AMBIITION
SUMMARY

STATISTICAL
SUMMARY

CLINICAL
SUMMARY

Figure 1: Mean Ibuprofen Serum Levels

#116-11-10839

N = 17

