CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74931

BIOEQUIVALENCY REVIEW(S)

DEC 23 1996

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Ibuprofen Tablets
200 mg
ANDA #74-931
Reviewer: Moheb H. Makary
WP 74931SDW.796

Novopharm Limited
Ontario, Canada
Submission date:
July 31, 1996

Review of Bioequivalence Studies, Dissolution Data and waiver request

I. Objective:

The firm has submitted the following bioequivalence studies:

1. Three-way, single-dose, fasting bioavailability study on Ibuprofen 200 mg Tablets using the following lots:

a. Novopharm Ibuprofen Tablets USP, 200 mg (capsule- shaped), lot #3014PD (manufactured using Ibuprofen raw materiål from

b. Novopharm Ibuprofen Tablets USP, 200 mg (caplet, brown), lot #3009PD (manufactured using Ibuprofen raw material from
c. Innovator product, Nuprin^{R} 200 mg Tablets (capsule- shaped), lot #503174.

2. Three-way, single-dose, post-prandial bioavailability study on Ibuprofen 200 mg Tablets using the following lots:

a. Novopharm Ibuprofen Tablets USP, 200 mg (capsule-shaped), lot #3014PD (manufactured using Ibuprofen raw material from

b. Innovator product, Nuprin^{R} 200 mg Tablets(capsule- shaped), lot #503174.

Currently the firm is only proposing as the manufacturer of Ibuprofen raw material. Therefore, all data pertaining to biostudy lot #3009PD is for investigational purpose only.

The firm requested a waiver of the in vivo study requirements for its Ibuprophen Tablets, 200 mg (round).

II. Introduction:

Ibuprofen is a propionic acid derivative with analgesic, antipyretic and anti-inflammatory activities. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under the serum drug concentration vs time curve. Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the

last dose. Nuprin[R] (Bristol-Myers) is an OTC product containing ibuprofen 200 mg and is indicated for the temporary relief of minor aches and pains associated with the common cold. The usual adult dosage is 1 tablet every 4 to 6 hours, and may be increased to 2 tablets but not exceeding 6 tablets in 24 hours.

III. Study-1663 For Single Dose Fasting Bioequivalence Of Novopharm's Ibuprofen 200 mg Tablets

site:

Analytical site:

Investigators:

Study date: Period I: February 3, 1996
Period II: February 10, 1996
Period III: February 17, 1996

Sample analysis: Sample analysis began on February 27, 1996 and was completed on March 28, 1996.

Study design: A single-dose, randomized, Three-treatment, Three-period crossover design.

Subjects: Forty (40) healthy male subjects enrolled and completed the study.

Selection criteria: Subjects selected for the study met the following acceptance criteria:

1. Ages 18 - 45 years, ± 10% of the ideal weight for his height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
3. No concurrent illness, acute or chronic diseases or history of serious cardiovascular, pulmonary, endocrine, immunologic, dermatologic, renal, G.I., hepatic, hematologic, neurologic, or psychiatric disease.
4. Negative for drug of abuse and HIV.

5. No history of hypersensitivity to ibuprofen or other nonsteroidal anti-inflammatory drugs.

Restrictions:

1. No ingestion of any alcohol, caffeine or xanthine-containing food or beverage within the 48 hours prior to initial dose of study medication.
2. No Rx or OTC drugs beginning 14 days prior to the study.

Dose and treatment: All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:

Test Products:

a) 1x200 mg Ibuprofen Brown FC Tablet (caplet) (Novopharm), lot #3014PD, batch size tablets, Manufacturing Date 1/12/96, potency %, content uniformity (%CV=0.4).

b) 1x200 mg Ibuprofen Brown FC Tablet (Novopharm), lot #3009PD, batch size (not reported), Manufacturing Date 1/12/96, potency (not reported), content uniformity (not reported).

Reference Product:

c) 1x200 mg Nuprin^{R} Tablet (caplet) (Bristol-Myers Squibb), Exp. Sep 99, lot #503174, potency %.

Washout period: One week

Food and fluid intake: 1x200 mg Ibuprofen tablet of either test or reference product was administered with 240 mL of water following a 10 hour fast. Subjects continued fasting for 4.5 hours post-dose. Water intake was not permitted from 1 hour before and until 1 hour after the dose.

Blood samples: Blood samples were collected at: 0 (prior to dosing), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing. Plasma was extracted and stored in labeled tubes at -12°C pending assay.

Assay Methodology

Sensitivity:

Linearity:

Assay specificity:

Recovery:

Stability:

Precision &
Accuracy:

Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for ibuprofen. An analysis of variance (ANOVA) was applied to log-transformed bioequivalence parameters to determine any statistically significant differences between the drug formulations. The 90% confidence intervals were calculated for each bioequivalence parameter.

IV. In Vivo Results:

The study was conducted at
during the period of February 3 to 17, 1996. Forty (40) male subjects enrolled and completed the study.
Subject #17 experienced mild lightheadedness for 2 hours during period II of the study. No treatment was administered.

The plasma concentrations for ibuprofen are summarized in Table I.

Table I

Mean Ibuprofen Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x200 mg Ibuprofen Tablet Under Fasting Conditions
(N=40)

Time hr	A Novopharm Test Product Lot #3014PD ug/mL (CV%)	B Novopharm Test Product Lot #3009PD ug/mL (CV%)	C Bristol-Myers Squibb Reference Product Lot #503174 ug/mL (CV%)
0	0.00	0.00	0.00
0.25	2.58 (110.6)	2.78 (116.6)	3.40 (167)
0.50	6.70 (78.4)	7.74 (73.3)	10.01 (73.8)
0.75	9.51 (60.3)	10.37 (58.3)	12.70 (51.4)
1.00	12.11 (44.2)	11.94 (48.9)	13.25 (42.0)
1.25	13.39 (39.5)	12.66 (39.6)	13.63 (36.0)
1.50	13.83 (36.2)	12.85 (35.7)	13.61 (31.3)
1.75	13.88 (32.3)	12.78 (32.8)	13.54 (34.8)
2.00	13.21 (28.7)	12.02 (29.2)	12.57 (33.1)
2.33	12.07 (29.4)	11.51 (27.4)	11.41 (28.4)
2.67	10.77 (27.4)	10.59 (29.1)	10.47 (30.8)
3.00	9.92 (28.7)	9.97 (31.3)	9.65 (31.4)
4.00	7.75 (39.3)	7.63 (41.1)	6.93 (34.5)
6.00	3.30 (41.5)	3.31 (42.5)	3.05 (40.7)
8	1.63 (41.6)	1.68 (47.7)	1.60 (50.2)
10	0.86 (47.5)	0.89 (56.9)	0.86 (55.6)
12	0.47 (49.0)	0.51 (62.8)	0.50 (62.1)
16	0.17 (62.2)	0.18 (83.6)	0.18 (82.9)
24	0.00 (632.5)	0.03 (493.5)	0.02 (345)

Pharmacokinetic Parameters

	A Test	B Test	C Reference	90% CI log-transf A vs C
AUC(0-t) (ug.hr/mL)	60.99(20)	60.55(23)	60.85(22)	97.7-103.4
AUCinf (ug.hr/mL)	61.68(20)	61.55(23)	61.36(22)	97.6-103.3
Cmax (ug/mL)	17.28(17)	16.40(19)	18.63(23)	88.4-100.1
Tmax (hr)	1.56	1.71	1.37	
Kel(1/hr)	0.29	0.28	0.27	
t1/2 (hr)	2.50	2.76	2.65	

1. For Novopharm test product (lot #3014PD), the means AUC(0-t), AUCinf and Cmax values are 0.23%, 0.52% and 7.2 higher and lower, respectively, than those for the reference product values. The differences are not statistically significant and the 90% confidence intervals are within the acceptable range of % for log-transformed AUC(0-t), AUCinf and Cmax.

2. The ibuprofen plasma levels peaked at 1.75 and 1.25 hours for the test (lot #3014PD) and reference products, respectively, following their administration under fasting conditions.

V. Study #1664-1 For Single Dose post-prandial Bioequivalence Study

Objective: The objective of the study is to compare the relative bioavailability of Ibuprofen 200 mg Tablets (Novopharm) with that of Nuprin^{R} 200 mg Tablets (Bristol-Myers Squibb) in healthy male volunteers under-nonfasting conditions, and to compare the difference in plasma levels after dosing with the test product when dosed with and without food.

Study site: Same as Study #1663 above

Study date: Period I April 13, 1996
Period II April 20, 1996
Period III April 27, 1996

Study design: A single-dose, randomized, three-treatment, three-period, six-sequence crossover design.

Subjects: Twenty-one (21) healthy male subjects entered the study. Twenty (20) subjects completed the study. Subject #17 was dismissed prior to period II start due to a protocol deviation regarding the lockout period (the enrolment in the study prior to his date of eligibility

of 45 days after a blood donation).

Selection criteria: Same as Study #1663 above.

Washout period: One week

Dose and treatment: Treatment A:
1x200 mg Ibuprofen Tablet (Novopharm), lot #3014PD administered following a standard meal preceded by an overnight fast.

Treatment B:
1x200 mg Nuprin® Tablet (Bristol-Myers Squibb), lot #503174 administered following a standard meal preceded by an overnight fast.

Treatment C:
1x200 mg Ibuprofen Tablet (Novopharm), lot #3014PD, administered after an overnight fast.

Food and fluid intake: Subjects were required to fast overnight for 10 hours prior to dosing in each treatment phase. Subjects on regimen C ingested the tablet with 240 mL of water. Subjects on regimen A and B ingested the tablet with 240 mL of water within 5 minutes after completing a standardized high-fat breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice). At 4.5 and 9.5 hours post-drug, standardized xanthine-free meals were provided to the subjects. At 15 hours post-drug, a snack was provided to each subject. Water intake was not permitted for 1 hour before and 1 hour after dosing, but was allowed at all other times.

Blood samples: Same as in Study #1663.

Assay Methodology Same as in Study #1663.

Statistical Methods Same as in Study #1663.

VI. In Vivo Results:

The study was conducted at during the period of April 12 to 28, 1996. Twenty-one (21) male subjects entered the study. Twenty subjects successfully completed the clinical

portion of the study. One adverse event was reported during the study. Subject #10, period I (test product under fasting conditions) experienced moderate faintness. The subject was able to complete the study, and the treatment consisted of placing the subject in bed on his right side.

The plasma concentrations for ibuprofen are summarized in Table II.

Table II

Mean Ibuprofen Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x200 mg Ibuprofen Tablet Under Fasting and Nonfasting Conditions
(N=20)

Time hr	A Novopharm Test Product Lot #3014PD Nonfasting ug/mL (CV%)	B Bristol-Myers Squibb Reference Product Lot #503174 Nonfasting ug/mL (CV%)	C Novopharm Test Product Lot #3014PD Fasting ug/mL (CV%)
0	0.00	0.02 (447.2)	0.01 (311)
0.25	0.73 (174.8)	0.64 (179.0)	1.51 (75.4)
0.50	3.61 (113.5)	5.21 (112.4)	7.48 (65.1)
0.75	5.56 (92.0)	7.65 (87.8)	11.76 (63.7)
1.00	6.86 (70.0)	9.08 (70.1)	13.44 (54.9)
1.25	8.00 (55.6)	10.53 (46.4)	13.73 (42.6)
1.50	8.72 (45.9)	11.53 (36.8)	14.10 (33.7)
1.75	9.15 (38.5)	11.47 (33.1)	13.79 (32.5)
2.00	9.46 (35.2)	11.05 (29.6)	13.59 (27.8)
2.33	10.08 (26.9)	10.20 (27.7)	13.56 (23.8)
2.67	10.20 (29.9)	10.08 (25.4)	11.99 (28.1)
3.00	10.11 (33.3)	9.47 (24.1)	10.64 (26.9)
4.00	8.65 (30.4)	7.71 (29.4)	8.58 (38.2)
6.00	4.26 (41.7)	3.58 (31.1)	3.55 (37.9)
8	2.05 (49.9)	1.74 (36.9)	1.74 (40.7)
10	1.14 (57.9)	0.95 (41.8)	0.94 (42.5)
12	0.59 (62.2)	0.54 (49.1)	0.49 (50.7)
16	0.20 (78.4)	0.17 (77.8)	0.16 (71.1)
24	0.01 (317.9)	0.00 (00.0)	0.01 (447)

Pharmacokinetic Parameters

	A Test	B Reference	C Test	A/B
AUC(0-t) (ug.hr/mL)	57.14(21)	56.27(20)	65.60(20)	1.02
AUCinf (ug.hr/mL)	57.87(21)	57.09(20)	66.37(20)	1.01
Cmax (ug/mL)	13.01(22)	14.39(26)	18.44(21)	0.90
Tmax (hr)	2.51	1.95	1.67	
Kel(1/hr)	0.29	0.30	0.30	
t1/2 (hr)	2.51	2.44	2.55	

1. For Novopharm test product, the means AUC(0-t), AUCinf and Cmax values are 1.5%, 1.4% and 9.5% higher and lower, respectively, than those for the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of for AUC(0-t), AUCinf and Cmax. The 90% confidence intervals are within the acceptable range of % for log-transformed AUC(0-t), AUCinf and Cmax.

2. The Ibuprofen plasma levels peaked at 1.5 and 2.67 hours for the reference and test products, respectively, following their administration under nonfasting conditions.

3. The mean Cmax of the test product was reduced by %, when dosed under nonfasting conditions compared to fasting conditions. This reduction in Cmax value is in agreement with the reference product's labeling which indicated that food intake, reduces the rate of absorption.

4. It should be noted that 0-hour (pre-dose) plasma ibuprofen concentrations of 0.35 ug/mL, 0.14 ug/mL and 0.11 ug/mL were detected for subject #3 on period II, subject #7 on period I and subject #9 on period III, respectively. After excluding these subjects from the statistical analysis for the reason mentioned above, the resulting ratios of the test mean to the reference mean under nonfasting conditions are as following:

	A/B
AUC(0-t)	1.02
AUCinf	1.01
Cmax	0.91

The ratios remain within the acceptable range.

VII. Formulations:

Novopharm's formulations for its capsule-shaped and round Ibuprofen 200 mg tablets is shown in Table III.

VIII. Dissolution:

Method:	USP 23 apparatus II (paddle) at 50 rpm
Medium:	900 mL of pH 7.2 phosphate buffer
Number of Tablets:	12
Test products:	Novopharm's Ibuprofen 200 mg Tablets, lot #3014PD(capsule-shaped) 200 mg Tablets, lot #3016PD(round)
Reference products:	Bristol-Myers Squibb's Nuprin^{R} 200 mg Tablets, lot #503174
Specifications:	NLT % in 60 minutes.

Dissolution testing results are shown in Table IV.

IX. Comments:

1. The firm's in vivo bioequivalence studies under fasting and nonfasting conditions are acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of % under fasting conditions. The ratios of the test mean to the reference mean were within the acceptable range of for AUC(0-t), AUCinf and Cmax under nonfasting conditions.

2. The in vitro dissolution testing submitted by the firm on its capsule-shaped and round ibuprofen 200 mg Tablets is acceptable.

X. Recommendations:

1. The bioequivalence studies conducted by Novopharm Limited, under fasting and nonfasting conditions on its Ibuprofen (capsule-shaped) Tablets, 200 mg, lot #3014PD, comparing it to Bristol-Myers Squibb's Nuprin^{R} 200 mg Tablets have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Novopharm's Ibuprofen Tablets, 200 mg is bioequivalent to the reference product, Nuprin^{R}, 200 mg Tablets, manufactured by Bristol-Myers Squibb.

2. The dissolution testing conducted by the firm on its Ibuprofen round and capsule-shaped Tablets, 200 mg, lots #3016PD and 3014PD, respectively, is acceptable. The formulation for the 200 mg round Tablet is similar to the 200 mg capsule-shaped Tablet which underwent acceptable bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 200 mg Ibuprofen

round Tablet is granted.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer pH 7.2 at ~37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than % of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 12/4/96

Concur: /S/ Date: 12/23/96
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/12-2-96 wp 74931SDW.796
cc: ANDA #74-931,original, HFD-658 (Makary), Drug File, Division File

Table IV. In Vitro Dissolution Testing

Drug (Generic Name): Ibuprofen Tablets
Dose Strength: 200 mg
ANDA No.: 74-931
Firm: Novopharm
Submission Date: July 31, 1996
File Name: 749321DW.796

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:X RPM: 50
No. Units Tested: 12
Medium: 900 mL of phosphate buffer pH 7.2
Specifications: NLT % in minutes
Reference Drug: Nuprin
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 3014PD Capsule- shaped Tablet Strength(mg) 200			Reference Product Lot # 503174 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	93.5		5.1	80.4		9.1
20	97.2		3.1	94.4		7.2
30	98.9		2.6	96.9		5.9
45	99.6		2.4	98.1		4.9
60	100.1		2.2	98.6		4.1
75	100.3		2.1	98.9		3.8

Sampling Times (Minutes)	Test Product Lot # 3016PD Round Tablet Strength(mg) 200			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	93.5		4.6			
20	98.5		3.0			
30	100.4		2.5			
45	101.7		2.0			
60	102.4		2.0			
75	102.7		2.0			