

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-350

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

4/21/05

MEMO TO FILE

FROM: WEI QIU, Ph.D.
TO: NDA 21-350
DATE: March 4, 2005
SUBJECT: Labeling Changes

The following proposed labeling changes in the submission dated March 4, 2005 are acceptable.

Under **CLINICAL PHARMACOLOGY** section **Pharmacokinetics** subsection

Absorption:

The second Paragraph states "TRIGLIDE 160 mg tablet exhibits a similar extent of absorption but 32% higher rate of absorption compared to the 200 mg micronized fenofibrate capsule under low-fat fed conditions."

Effect of Food on Absorption:

The first Paragraph states "Fenofibrate is insoluble in water and its bioavailability is optimized when taken with meals."

The second Paragraph states "The extent of absorption of TRIGLIDE (AUC) is comparable between fed and fasted conditions. Food increases the rate of absorption of TRIGLIDE approximately 55%."

Under **CLINICAL TRIALS** section

The first paragraph states "In a single-dose pharmacokinetics study in healthy volunteers, TRIGLIDE 160 mg tablet was shown to have comparable bioavailability to a single dose of 200 mg fenofibrate capsule, micronized."

Under **WARNINGS** section **Concomitant HMG-CoA Reductase Inhibitors (Statins)** subsection:



Comments: The biopharm reviewer concurs with the proposed labeling changes listed above.

The comments should be conveyed to the sponsor as appropriate.

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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/s/

Wei Qiu
4/20/05 01:38:17 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/21/05 01:53:47 PM
BIOPHARMACEUTICS

MEMO TO FILE

FROM: WEI QIU, Ph.D.
TO: NDA 21-350
DATE: January 28 and March 4, 2005
SUBJECT: Amendment (Complete Response to the Approvable Letter Dated December 14, 2004) and response to the Division request dated February 25, 2005

The sponsor, SkyePharma, submitted a response on January 28, 2005 to the Agency's Approvable Letter dated 14 December 2004 and a response on March 4, 2005 to the Division's information request dated February 25, 2005.

In these submissions, the sponsor included dissolution profiles of 1 x 160mg tablet from Lot #H904 (batch H569 in [redacted] bottle), dissolution profiles of 3 x 50 mg tablets and 1 x 50 mg tablet from Lots # H556, H565, and H976 (Table 1). Lot #H904 has a theoretical batch size of [redacted] tablets and the Lots #H556, 565, and 976 have the theoretical batch size of [redacted] tablets. The sponsor utilized the following recommended dissolution conditions:

Apparatus: USP Apparatus 2 (paddles)
 Speed: 50 rpm
 Temperature: 37°C ± 0.5°C
 Dissolution Volume: 900 mL
 Dissolution medium: 0.025 M SLS.

Table 1. Comparative Dissolution Profiles: Triglide Tablets 50 mg and 160 mg

	Time Interval	10 min	20 min	30 min	45 min	60 min	Metrics statics H904 vs 3 x 50mg		
							f1	f2	
160 mg tablet, Lot # H904 (batch H569 in [redacted] bottle) *	Mean of 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	% RSD								
	Minimum								
	Maximum								
3 x 50 mg tablet, Lot # H 556	Mean of 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10	66
	% RSD								
	Minimum								
	Maximum								
3 x 50 mg tablet, Lot # H 565	Mean of 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10	62
	% RSD								
	Minimum								
	Maximum								
3 x 50 mg tablet, Lot # H 976	Mean of 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6	69
	% RSD								
	Minimum								
	Maximum								
50 mg tablet, Lot # H 556	Mean of 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	% RSD								
	Minimum								
	Maximum								
50 mg tablet, Lot # H 565	Mean of 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	% RSD								
	Minimum								
	Maximum								
50 mg tablet, Lot # H 976	Mean of 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	% RSD								
	Minimum								
	Maximum								

min - minute; RSD - relative standard deviation, Nd - Not done

On average, both the 3 x 50 mg and 1 x 160 mg tablets dissolved rapidly with more than [redacted] in 20 minutes. The one 50 mg tablet dissolved more than [redacted] in 20 minutes. Thus the dissolution profiles of the three 50 mg tablets were similar to one 160 mg tablet. In addition, the 50 mg tablet is in the same dosage

form and is proportionally similar in its active and inactive ingredients to the 160 mg tablet. Therefore, the biowaiver request for the 50 mg tablet can be granted.

Based on the limited dissolution data provided for the 160 mg tablet (12 tablets from Lot #904), the dissolution specification of not less than $\frac{1}{2}$ (Q) at 30 minutes is recommended. Based on the dissolution data obtained from three lots of 50 mg tablets (Lots #H556, 565, 976), the dissolution specification of not less than $\frac{1}{2}$ (Q) at 20 minutes is recommended.

Comments: The biowaiver request for the 50 mg tablet can be granted. The following dissolution specifications are recommended:

50 mg: Not less than $\frac{1}{2}$ (Q = $\frac{1}{2}$) in 20 minutes

160 mg: Not less than $\frac{1}{2}$ (Q = $\frac{1}{2}$) in 30 minutes

The comments should be conveyed to the sponsor as appropriate.

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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/s/

Wei Qiu
4/7/05 04:08:03 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/12/05 10:30:10 AM
BIOPHARMACEUTICS

6/30/04

MEMO TO FILE

FROM: WEI QIU, Ph.D.
TO: NDA 21-350
DATE: March 31, 2004
SUBJECT: Amendment (Complete Response to the Approvable Letter)

On March 31, 2003, SkyePharma submitted a complete response to the Agency's Approvable Letter dated on April 24, 2002.

In this submission, the sponsor has included a final study report of FEN101-C25. The study results show that IDD®-P fenofibrate 160 mg has comparable bioavailability in terms of the extent of absorption (AUC) compared to 200 mg MF (Lipanthyl® 200 M) under low fat condition while the rate of absorption (Cmax) of IDD®-P was higher than Lipanthyl® 200M. However, it should be noted that the batch size used in this study is extremely small, while the full scale size for the 160 mg strength is tablets. Therefore, this study is not acceptable.

The sponsor is recommended to conduct another study to address the relative bioavailability compared with RLD Tricor® tablets, food effect, and dosage form equivalence using a batch size of at least of the commercial scale.

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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/s/

Wei Qiu
6/30/04 03:21:49 PM
BIOPHARMACEUTICS

Hae-Young Ahn
6/30/04 03:34:03 PM
BIOPHARMACEUTICS

MEMO TO FILE

FROM: WEI QIU, Ph.D.
TO: NDA 21-350
DATE: January 28, 2005
SUBJECT: Amendment (Complete Response to the Approvable Letter Dated December 14, 2004)

The sponsor, SkyePharma, submitted a response on January 28, 2005 to the Agency's Approvable Letter dated 14 December 2004.

The Agency's Approvable Letter stated "With limited dissolution data provided, it appeared that the 160 mg tablets dissolved similarly in 0.025 M SLS [REDACTED] media. Therefore, the dissolution method using the lower SLS concentration of 0.025 M is recommended. Since the dissolution data of 50 mg tablets using 0.025 M is lacking, provide data for three batches [REDACTED] (batch) of the 50 mg strength under the condition of USP apparatus 2 at 50 rpm in 0.025 M SLS medium. The biowaiver for the 50 mg tablets will be determined based on similarity between the dissolution profiles of the 50 mg and 160 mg tablets using USP Apparatus 2 at 50 rpm in 0.025 M SLS medium."

In this submission, the sponsor has included dissolution profiles of 1 x 160mg from Lot #H904 (batch H569 in [REDACTED] bottle) and 3 x 50 mg from Lots # H556, H565, and H976. To evaluate the similarity of dissolution profiles between strengths and set appropriate dissolution specification for the 50 mg tablets, dissolution data for 1x 50 mg tablet are required. In addition, critical information of these tested batches including formulation, manufacturing process, batch sizes were not provided in the biopharm section.

Thus, the sponsor is recommended to provide dissolution profiles for three batches [REDACTED] (batch) of 1 x 50 mg tablet using USP Apparatus 2 at 50 rpm in 0.025 M SLS medium. Additionally, relevant information including formulation, manufacturing process, and batch sizes for 160 mg tablet Lot #H904 (batch H569), 50 mg tablet Lots #H556, #H565, and #H976 should be provided. If the sponsor choose to use different batches to evaluate the dissolution profile of 1 x 50 mg tablet, the same information should be provided for these additional batches.

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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/s/

Wei Qiu
2/25/05 01:19:15 PM
BIOPHARMACEUTICS

Hae-Young Ahn
2/25/05 01:32:12 PM
BIOPHARMACEUTICS

MEMO TO FILE

FROM: WEI QIU, Ph.D.
TO: NDA 21-350
DATE: October 14, 2004
SUBJECT: Additional Dissolution Method Validation and Data

On March 31, 2004 SkyPharma submitted a complete response to the Agency's Approvable Letter dated April 24, 2002 for IDD®-P fenofibrate tablets for the indication of treatment of hypertriglyceridemia. This amendment stated that the formulation was changed and manufacturing process was changed _____

During the review of this NDA, it was found that the sponsor conducted dissolution studies using the dissolution method (USP Apparatus 2 at 50 rpm in _____ sodium lauryl sulfate medium) for the previous formulation. To optimize the dissolution method for the current product, the sponsor is recommended to investigate two other conditions (e.g., lower SLS concentrations). The sponsor must submit individual dissolution profiles for tablets from 3 batches \ _____ batch).

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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/s/

Wei Qiu
10/18/04 08:33:55 AM
BIOPHARMACEUTICS

Hae-Young Ahn
10/18/04 09:54:21 AM
BIOPHARMACEUTICS

MEMO TO FILE

FROM: WEI QIU, Ph.D.
TO: NDA 21-350
DATE: July 30, 2004
SUBJECT: Response to FDA Information Request Letter

On July 30, 2004, SkyePharma submitted a response to FDA Information Request Letter dated July 2, 2004.

In this submission, the sponsor included a final study report of FEN101-C1-001 entitled "Comparative Bioavailability of IDD-P Fenofibrate Product (tfl1) 160 mg Tablet Administered Under Different Food Conditions with Micronized Fenofibrate 200 mg Capsule Taken Under Low-fat Fed Conditions".

During the review process, it was found that on page 7 of the study report, it was indicated that the reference product was Lypanthyl® 200M, fenofibrate (micronized) 200 mg capsules manufactured by Laboratoires Fournier S.A., France. However, on page 38, Section 9.4.2 Identity of investigation product(s), it was indicated that the reference product was Lipanthyl® 200M, fenofibrate 200 mg capsule manufactured by Laboratoires Fournier, S.A., France. The capsules were described as opaque, pink, no imprinted capsules.

The sponsor is encouraged to clarify what product was used as reference in study FEN101-C1-001. It was also noted that Lipanthyl® 200M capsules used as reference product in study FEN101-C25 had orange color. This information was found on page 37 of the study report of FEN101-C25. The sponsor is recommended to explain the difference in the appearance of the reference capsules used in studies FEN101-C1-001 and FEN101-C25. Moreover, the sponsor needs to explain why all the reference products had no imprint on the capsules.

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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Wei Qiu
10/8/04 09:29:01 AM
BIOPHARMACEUTICS

Hae-Young Ahn
10/13/04 02:27:05 PM
BIOPHARMACEUTICS

MEMO TO FILE

FROM: WEI QIU, Ph.D.
TO: NDA 21-350
DATE: March 31, 2004
SUBJECT: Amendment (Complete Response to the Approvable Letter)

On March 31, 2003, SkyePharma submitted a complete response to the Agency's Approvable Letter dated on April 24, 2002.

In this submission, the sponsor has included a final study report of FEN101-C25. The study results show that IDD®-P fenofibrate 160 mg has comparable bioavailability in terms of the extent of absorption (AUC) compared to 200 mg MF (Lipanthyl® 200 M) under low fat condition while the rate of absorption (Cmax) of IDD®-P was higher than Lipanthyl® 200M. However, it should be noted that the batch size used in this study is extremely small while the full scale size for the 160 mg strength is tablets. Therefore, this study is not acceptable.

The sponsor is recommended to conduct another study to address the relative bioavailability compared with RLD Tricor® tablets, food effect, and dosage form equivalence using a batch size of at least of the commercial scale.

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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Wei Qiu
6/30/04 03:21:49 PM
BIOPHARMACEUTICS

Hae-Young Ahn
6/30/04 03:34:03 PM
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-350	Submission Date(s): March 31, 2004; July 30, 2004; November 16, 2004
Brand Name	IDD [®] -P fenofibrate tablets
Generic Name	fenofibrate
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
OND Division	Division of Metabolic and Endocrine Drug Products
Sponsor	SkyePharma
Relevant IND(s)	60,743
Submission Type	Response to Approvable letter and Amendment
Formulation; Strength(s)	Oral tablets; 50 and 160 mg
Indication	Treatment of hypertriglyceridemia

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed the complete response to the Agency's Approvable Letter and several amendments to Information Request (IR) letters submitted on March 31, 2004; July 30, 2004; and November 16, 2004 and finds them acceptable provided that the sponsor submits dissolution data of 50 mg tablets using 0.025 M Sodium Lauryl Sulfate (SLS) medium and

satisfactory agreement is reached between the sponsor and the Agency regarding the dissolution method and specification. Recommendation, comments, and labeling comments should be conveyed to the sponsor as appropriate.

Comments:

1. With limited dissolution data provided by the sponsor, it appeared that the 160 mg tablets dissolved similarly in 0.025 M SLS [redacted] media. Therefore, the dissolution method using the lower SLS concentration of 0.025 M is recommended. Since the dissolution data of 50 mg tablets using 0.025 M SLS was lacking, the sponsor is recommended to provide data for 3 batches [redacted] (batch) of the 50 mg strength under the condition of USP Apparatus 2 at 50 rpm in 0.025 M SLS medium. The biowaiver for the 50 mg tablets will be granted based on the similarity between the dissolution profiles of the 50 mg and 160 mg tablets using USP Apparatus 2 at 50 rpm in 0.025 M SLS medium.
2. From biopharmaceutical point of view, the relative bioavailability study (FEN101-C1-001) is adequate to address the relative bioavailability of IDD[®]-P compared to micronized fenofibrate capsule. Thus, this study is acceptable unless the Agency has some concerns regarding the legal issues of using foreign products as a reference. However, the sponsor is highly recommended to use a US approved product as a reference in the future.

1.2 Phase IV Commitments

Not Applicable.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Relative Bioavailability of IDD[®]-P Fenofibrate Tablet Compared to Reference Micronized Capsule (Lipanthyl[®] 200M)

The extent of absorption of IDD[®]-P fenofibrate tablet 160 mg is comparable to that of micronized fenofibrate capsule 200 mg under low-fat fed conditions. However, the rate of absorption of IDD[®]-P fenofibrate tablet is [redacted] higher than that of micronized fenofibrate capsule. Ratios of (IDD[®]-P fenofibrate tablet 160 mg /micronized fenofibrate capsule 200 mg) of least-squares means for AUC_{0-t}, AUC_{0-∞}, and C_{max} are 108%, 97%, and 132.1%, respectively. The 90% geometric confidence intervals of AUC_{0-t} and AUC_{0-∞} are within the 80% - 125% range while the 90% CI for C_{max} is beyond the 80% - 125% range. This reviewer consulted with the Dr. Mary Parks, Deputy Director of DMEDP, regarding the [redacted] higher C_{max} value exhibited by IDD[®]-P fenofibrate 160 mg tablet. Dr. Parks stated that the [redacted] higher C_{max} would not cause safety concern.

Food Effect

Food has little effect on the extent of absorption but causes a [redacted] increase in the rate of absorption. The effect on the rate of absorption is not influenced by fat content. Ratios (low-fat fed/fasting) of least-squares means for AUC_{0-t}, AUC_{0-∞}, and C_{max} are 114.2%, 110.5%, and 154.9%, respectively. Ratios (high-fat fed/fasting) of least-squares means for AUC_{0-t}, AUC_{0-∞}, and C_{max} are 119.5%, 113.9%, and 151.5%, respectively. The 90% confidence interval of AUC_{0-∞} is within the 80% - 125% range while the 90% confidence intervals for AUC_{0-t} and C_{max} are beyond the 80% - 125% range.

2 Question Based Review

2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The original NDA was submitted on June 22, 2001. The Division issued an Approvable Letter on April 24, 2002 due to product instability at room temperature. On March 31, 2004, the sponsor submitted a complete response amendment reflecting a formulation change and process change [REDACTED]. The amendment contains a relative bioavailability study FEN101-C25 using the new formulated products manufactured by the [REDACTED] process. However, this study was not acceptable because the batch size of 363 tablets was inadequate to represent the commercial batch size of [REDACTED] tablets. The Division sent an Information Request letter on July 2, 2004 to request additional biopharmaceutical information. On July 30, 2004, the sponsor submitted an amendment where a BE study FEN101-C1-001 was included in the Clinical Pharmacology section. The batch size of [REDACTED] tablets for the product (Lot H904) used in study FEN101-C1-001, the same as the commercial batch size, is adequate.

2.2 General Clinical Pharmacology

Not applicable.

2.3 Intrinsic Factors

Not applicable.

2.4 Extrinsic Factors

Not applicable.

2.5 General Biopharmaceutics

1. What is the relative bioavailability of IDD[®]-P fenofibrate tablet compared to micronized fenofibrate capsule?

The IDD[®]-P fenofibrate 160 mg tablet has similar extent of absorption but [REDACTED] higher rate of absorption compared to the 200 mg micronized capsule under low-fat fed conditions. The low-fat fed condition used in this relative bioavailability study is appropriate because the reference drug is labeled as to be taken with meals to increase bioavailability.

Study FEN101-C1-001 was a single dose, open-label, randomized, four-treatment, four period, four-sequence crossover study. This study was conducted between Feb. 2004 and March 2004. Subjects were given either IDD[®]-P fenofibrate 1 x 160 mg tablet under fasting (Treatment C), low-fat fed (Treatment A), or high-fat fed (Treatment B) conditions or 1 x 200 mg capsule of Lipanthy[®] 200M (Lot #76769) under low-fat fed (Treatment D) conditions. The reference product, Lipanthy[®] 200M, fenofibrate (micronized) 200 mg capsule were manufactured by Laboratories Fournier S.A. in France. The concentration-time profiles of all treatments are presented in **Figure 1**. The pharmacokinetic parameters for IDD[®]-P fenofibrate tablet 160 mg and Lipanthy[®] 200M, fenofibrate (micronized) 200 mg capsule under low-fat fed conditions are summarized in **Table 1**.

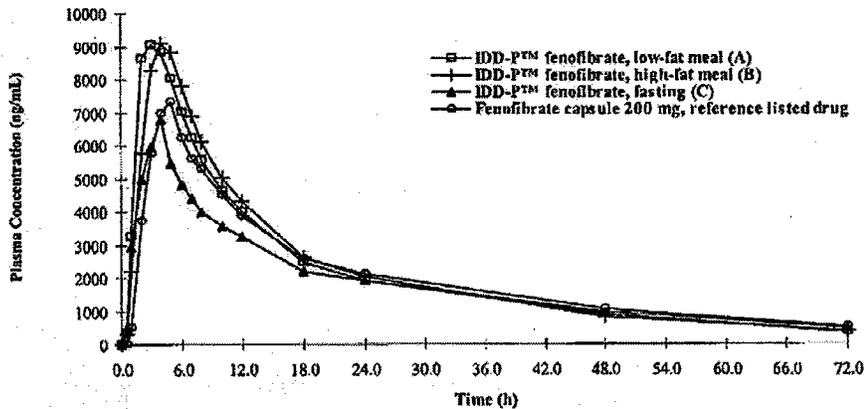


Figure 1. Fenofibric Acid Concentration-Time profiles.

Table 1. Pharmacokinetic Parameters for IDD[®]-P fenofibrate tablet 160 mg (A) and Lipanthyl[®] 200M, fenofibrate (micronized) 200 mg capsule (D) under low-fat fed conditions (N=16).

Parameter	IDD [®] -P fenofibrate tablet 160 mg (A) low fat fed			Lipanthyl [®] 200 M micronized capsule 200 mg (D) low fat fed		
	Mean	SD	CV(%)	Mean	SD	CV(%)
AUC _{0-t} (ng.h/mL)	150985.4	64057.3	42.4	140104.5	59652.4	42.6
AUC _{0-∞} (ng.h/mL)	166967.2	82212.1	49.2	172435.8	83518.7	48.4
C _{max} (ng/mL)	10554.7	1880.2	17.8	8084.0	2187.6	48.4
T _{max} * (h)	2.5	2.0	--	5.0	1.0	--
T1/2 (h)	18.8	5.6	29.6	22.8	11.8	51.8

*For t_{max}, median is presented.

Statistical analyses (Table 2) showed that the ratios (A/D) of least-square means for AUC_{0-t}, AUC_{0-∞}, and C_{max} were 108.03%, 96.96%, and 132.08%, respectively. IDD[®]-P fenofibrate tablet 160 mg demonstrated a similar extent of absorption but a higher rate of absorption compared to Lipanthyl[®] 200M.

Table 2. Treatment comparison for IDD[®]-P fenofibrate tablet 160 mg (A) and Lipanthyl[®] 200M, fenofibrate (micronized) 200 mg capsule (D) under low-fat fed conditions.

Parameter	Ratio of LS Means (A/D)	90% Confidence Interval
AUC _{0-t}	108.0%	96.6-120.9%
AUC _{0-∞}	97.0%	91.6-102.7%
C _{max}	132.1%	116.6-149.6%

Comments: It was noted that the sponsor failed to use an US approved product Tricor[®] micronized capsule as the reference product. Instead, an European product Lipanthyl[®] 200M (Lot #76769) was utilized in this study. In a submission dated 24 February 2003, the sponsor provided a letter (See Appendix 4.2) issued by Fournier Laboratoires, manufacturer of both Tricor[®] and Lipanthyl[®] products. Within the letter, it was confirmed that the two products Lipanthyl[®] 200 M (batch 66467) and Tricor[®] 200 mg capsules are:

- identical in term of qualitative and quantitative composition (at the exception of the logo printing on the capsule shell),
- manufactured with the same manufacturing process, equipment and adhere to the same in process controls.

In addition, the letter indicated that Lipanthy[®] 200M had been tested in accordance with methodologies defined in the US NDA for Tricor[®] 200 mg and found compliant to all specifications.

From biopharmaceutical point of view, this study is adequate to address the relative bioavailability of IDD-P compared to micronized fenofibrate capsule. Thus, this study is acceptable unless the Agency has some concerns regarding the legal issues of using foreign products as a reference. In the future, the sponsor is highly recommended to a US approved product as a reference.

2. Is the dissolution method adequately validated?

The proposed dissolution method is not adequately justified and the Agency recommends USP Apparatus 2 at 50 rpm in 0.025 M SLS medium.

The dissolution data of 50 mg and 160 mg tablets using the dissolution method (USP apparatus 2 at 50 rpm in 0.025 M SLS medium) that was agreed for the previous formulation are shown in Table 3. On average, the 160 mg tablets dissolve more than 80% in 20 minutes. All 50 mg tablets dissolved more than 80% in 20 minutes. Three 50 mg tablets dissolved more than 90% at 20 minutes. Both strengths dissolved rapidly under this condition.

Table 3. Drug product dissolution test results

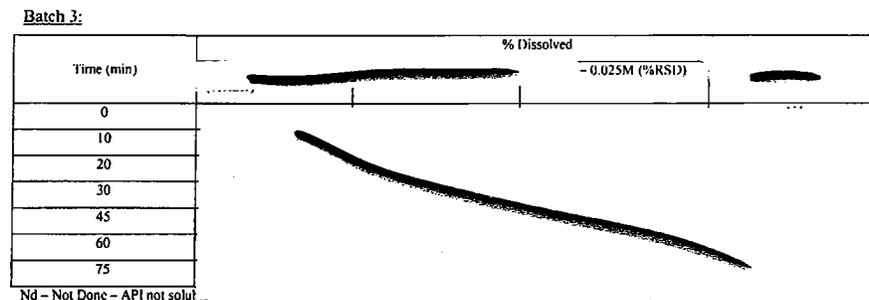
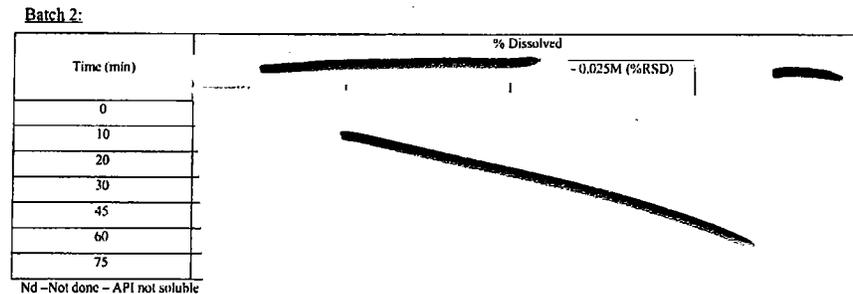
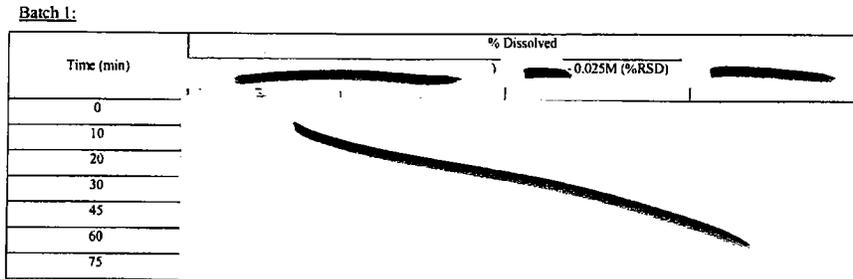
	Time Interval	10 min	20 min	30 min	45 min	60 min
160 mg tablet, Lot # H569	Mean of 12	80	90	95	98	100
	% RSD					
	Minimum					
	Maximum					
160 mg tablet, Lot # H570	Mean of 12	80	90	95	98	100
	% RSD					
	Minimum					
	Maximum					
160 mg tablet, Lot # H571	Mean of 12	80	90	95	98	100
	% RSD					
	Minimum					
	Maximum					
3 x 50 mg tablet, Lot H566	Mean of 12	80	90	95	98	100
	% RSD					
	Minimum					
	Maximum					
50 mg tablet, Lot # H708	Mean of 6	80	90	95	98	100
	% RSD					
	Minimum					
	Maximum					
50 mg tablet, Lot # H709	Mean of 6	80	90	95	98	100
	% RSD					
	Minimum					
	Maximum					
50 mg tablet, Lot # H710	Mean of 6	80	90	95	98	100
	% RSD					
	Minimum					
	Maximum					

Due to the formulation change and manufacturing process change, the sponsor was asked to investigate two other conditions (e.g., lower SLS concentrations) to optimize the dissolution method for the current product. The sponsor submitted dissolution data for 3 batches of 160 mg tablets under lower SLS concentrations, 0.025 M SLS (Table 4). For all the 3 batches, the dissolution profiles are similar between 0.025 M SLS, implying the 0.025 M SLS is unnecessary. On the other hand, the 160 mg tablets did not dissolve completely after 60 minutes

Thus, among the three conditions examined, the 0.025 M SLS would be the most appropriate based on the provided data.

Comments: Although the dissolution data for the 50 mg tablets were not provided using 0.025 M SLS, it is assumed that the 50 mg tablets have at least the dissolution rate of the 160 mg tablets based on the dissolution test results provided in **Table 3**. However, the sponsor is recommended to submit the dissolution data for 50 mg tablets using 0.025 M SLS medium.

Table 4. Dissolution of 160 mg tablets using different concentrations of SLS



3. What data support or do not support a waiver of in vivo BE data for the 50 mg strength?

The 50 mg tablet is in the same dosage form and is proportionally similar in its active and inactive ingredients to the 160 mg tablet. On average, both the 50 mg and 160 mg tablets dissolved more than 80% in 20 minutes using 0.025 M SLS. The comparison between the dissolution profiles of these strengths using 0.025 M SLS was not conducted because of lacking data for the 50 mg tablets. The biowaiver for the 50 mg tablets will be considered once the sponsor submits the dissolution data for the 50 mg tablet using 0.025 M SLS and similarity of dissolution profiles between the 50 mg and 160 mg tablets is adequately justified.

The IDD[®]-P fenofibrate 50 mg and 160 mg tablets are proportionally similar in its active and inactive ingredients (Table 5).

Table 5. Quantitative Composition of IDD[®]-P Fenofibrate Tablets 50 mg and 160 mg

Ingredient	Quantity per 50 mg tablet (mg)	Quantity per 160 mg tablet (mg)
Fenofibrate	50.000	160.000
Egg lecithin		
Sodium phosphate monobasic		
Mannitol		
Maltodextrin		
Carboxymethylcellulose sodium		
Lactose monohydrate		
Croscopovidone		
Croscarmellose sodium		
Sodium lauryl sulfate		
Colloidal silicon dioxide		
Magnesium stearate		
Total		

4. What is the effect of food on the bioavailability of IDD[®]-P fenofibrate tablet?

Both low-fat and high-fat meals have little effect on the extent of absorption ($AUC_{0-\infty}$) of IDD[®]-P fenofibrate tablet. However, low-fat and high-fat meals increase the rate of absorption (C_{max}) of IDD[®]-P fenofibrate tablet by ██████████, respectively. Therefore, the food effect on the rate of absorption is independent of fat content.

The food effect was assessed in study FEN101-C1-001 where healthy subjects received IDD[®]-P fenofibrate tablet 160 under fasting (C), low-fat fed (A), and high-fat fed (B) conditions. Results are shown in Figure 1 and Tables 6. Statistically analysis is presented in Table 7. Ratios (A/C) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 114.2%, 110.9%, and 154.9%, respectively. Ratios (B/C) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 119.5%, 113.9%, and 151.5%, respectively. Food exhibited no effect on the extent of absorption but increased the rate of absorption approximately ██████████.

Table 6. Pharmacokinetic Parameters for IDD[®]-P Fenofibrate Tablet 160 mg under Fasting (C), Low-fat Fed (A), and High-fat Fed (B) Conditions.

Parameters	IDD [®] -P fenofibrate tablet 160 mg (C) Fasting			IDD [®] -P fenofibrate tablet 160 mg (A) Low-fat Meal			IDD [®] -P fenofibrate tablet 160 mg (B) High-fat Meal		
	Mean	SD	CV(%)	Mean	SD	CV(%)	Mean	SD	CV(%)
AUC_{0-t} (ng.h/mL)	131350.9	55970.6	42.6	150985.4	64057.3	42.4	157334.6	65284.0	41.5
$AUC_{0-\infty}$ (ng.h/mL)	151367.2	76147.5	50.3	166967.2	82212.1	49.2	170504.8	78757.2	46.2
C_{max} (ng/mL)	6932.8	2596.8	37.5	10554.7	1880.2	17.8	10380.9	2100.1	20.2
T_{max} (h)	4.00	1.00	--	2.5	2.0	--	3.0	1.2	--
$T_{1/2}$ (h)	22.7	7.2	31.5	18.8	5.6	29.6	18.1	5.7	31.4

*For T_{max} , median is presented.

Table 7. Treatment Comparisons for IDD-P Fenofibrate Tablet 160 mg under Fasting (C), Low-fat Fed (A), and High-fat Fed (B) Conditions.

Parameters	Treatment comparison	Ratio of LS means	90% Confidence interval
AUC _{0-t}	Low-fat fed (A) vs fasting (C)	114.2%	102.2-127.8%
	High-fat fed (B) vs. fasting (C)	119.5%	106.8-133.7%
AUC _{0-∞}	Low-fat fed (A) vs fasting (C)	110.5%	104.3-117.0%
	High-fat fed (B) vs. fasting (C)	113.9%	107.5-120.6%
C _{max}	Low-fat fed (A) vs fasting (C)	154.9%	136.8-175.4%
	High-fat fed (B) vs. fasting (C)	151.5%	133.8-171.6%

2.6 Analytical Section

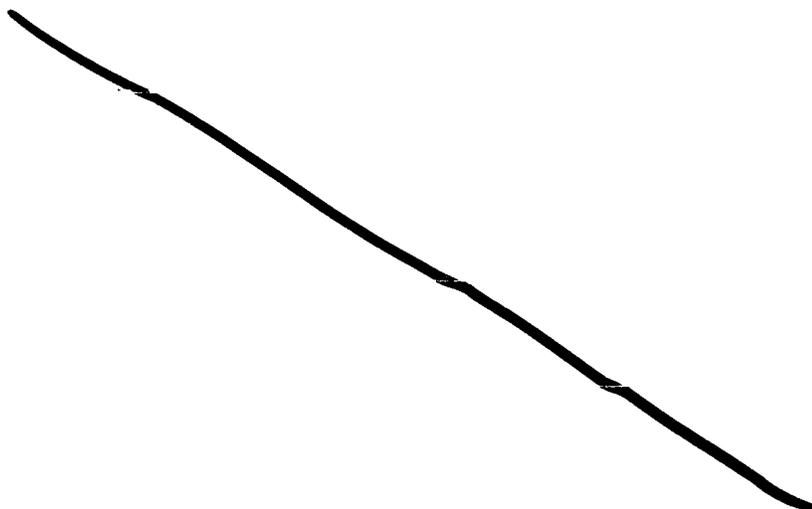
1. What bioanalytical methods are used to assess concentrations?

A HPLC method was utilized for the determination of fenofibric acid in human plasma.

Calibration curve ranged from 50 to 20000 ng/mL. Lower limit of detection was 3.12 ng/mL and lower limit of quantitation was 49.93 ng/mL. The maximum study sample storage period from first blood draw to last sample analysis is 49 days. Fenofibric acid is stable in plasma under storage conditions at a nominal temperature of -20°C for 185 days. QC samples have the concentrations of 150.57, 301.14, 6022.88, and 14053 ng/mL. The between-run accuracy (% Nominal) and precision (CV%) for QC samples ranged from 101.95 to 106.70% and from 2.65% to 4.53%, respectively. This analytical method is adequately validated.

3 Detailed Labeling Recommendations

Pharmacokinetics





4 Appendix

4.1 Individual Study Synopsis

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2. Study Synopsis

Name of Sponsor/Company: SkyePharma Inc.	
Name of finished Product: IDD-P™ Fenofibrate	
Name of Active Ingredient: Fenofibrate	
Title of Study: Comparative Bioavailability of IDD-P™ Fenofibrate Product 160 mg Tablet Administered Under Different Food Conditions with Fenofibrate 200 mg Capsules, Reference Listed Drug, Taken Under Low-Fat Fed Conditions	
Investigator(s): Investigator: _____ Sub-Investigator (s): _____	
Study Centre(s): _____	
Publication (reference): None at the date of this report	
Study Period (IRB approval to last scheduled visit): February 2, 2004, to March 27, 2004	Phase of Development: Phase I study
Scheduled dosing days: Period 1: February 19, 2004 Period 2: February 29, 2004 Period 3: March 10, 2004 Period 4: March 20, 2004	Type of Study: Single dose pharmacokinetic- Comparative bioavailability
Objectives: To assess and compare the rate and extent of absorption of IDD-P™ fenofibrate 160 mg tablet taken under different food conditions (fasting, low-fat fed, and high-fat fed) with Fenofibrate capsule 200 mg, reference listed drug taken after a low-fat meal.	

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Methodology:

This was a single-center, single dose, open-label, randomized, four-treatment, four-period, four-sequence crossover study to assess and compare the rate and extent of absorption of IDD-PTM fenofibrate 160 mg tablet taken under different food conditions (fasting, low-fat fed, and high-fat fed) with Fenofibrate capsule 200 mg, reference listed drug taken after a low-fat meal. Doses were separated by washout periods of 10 days. Twenty (20) healthy, adult male non-smokers were enrolled in this study. Subjects were confined from early evening on the day prior to dosing, until after the 24.0-hour post-dose blood draw in each period.

Subjects were administered 1 tablet of IDD-PTM fenofibrate 160 mg (treatments A, B, and C) or 1 capsule of Fenofibrate capsule 200 mg, reference listed drug (treatment D). Subjects receiving treatment C fasted for at least 10 hours prior to drug administration. Subjects receiving treatments A, B, and D fasted for at least 9.5 hours prior to being served an assigned test meal (low-fat [treatments A and D] or high-fat meal [treatment B]). These meals were consumed over an interval of 25 minutes and completed 5 minutes prior to study drug administration.

All blood samples were drawn into blood collection tubes (1 x 7 mL) containing EDTA K3, prior to drug administration and 0.500, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 18.00, 24.00, 48.00, and 72.00 hours post-dose, in each period. All blood samples were collected via a dead-volume intravenous catheter (when possible) and via direct venipuncture otherwise.

Blood samples were _____ for at least 10 minutes at approximately 4°C. Two aliquots of at least 1.2 mL (when possible) of plasma were dispensed into _____ tubes as soon as possible, before being transferred to a -20°C±5°C freezer, pending analysis. Less than 50 minutes passed between the time of each blood draw and the start of _____ and less than 180 minutes passed between the start of _____ processing.

Number of Subjects (planned and analyzed):

Of the 20 healthy, male non-smokers who were dosed, 17 completed the study. Two (2) subjects (Subjects No. 01 and 13) elected to withdraw from the study prior to Periods 3 and 4, respectively, for personal reasons. Subject No. 05 was withdrawn from the study, due to a positive drug screen result prior to Period 2 drug administration. Therefore, 17 of the 20 subjects were considered as having completed the clinical portion and the data of 16 subjects were used for the pharmacokinetic analysis, as specified in the protocol. Safety analysis and procedures were performed for the 20 subjects who were dosed.

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Inclusion and Exclusion Criteria:

Inclusion Criteria:

- 18 to 55 year old male subjects;
- BMI < 30;
- deemed "normal" following a comprehensive clinical assessment (detailed medical history, complete physical examination, and ECG) and laboratory investigations (hematology, biochemistry, urinalysis), the results of which had to be within the normal range and/or clinically acceptable for healthy subjects;
- non-smoker, non-tobacco user for at least 3 months;
- negative urine drug screen and alcohol urine or breath test;
- subjects with "normal" dietary habits (i.e. no restrictive regimen) and willing to eat the test meal;
- informed subjects accepting the study constraints and restrictions and having signed the informed consent.

Exclusion Criteria:

- history of major medical/psychiatric illness or surgery which, in the judgement of the Investigator, put the subject "at risk" or was likely to modify his handling of the study drug;
- history of renal, hepatic, and/or gallbladder disease;
- suffering from any acute or chronic systemic disease or disorder;
- history of hypersensitivity or intolerance to fibrate drugs;
- regular use of sedatives, hypnotics, tranquilizers, or any other addictive substances;
- signs, symptoms and laboratory test values outside the clinically acceptable "normal range" for healthy subjects: ECG abnormalities (clinically significant) or vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm) at screening;
- history or evidence of acute or chronic alcohol abuse (>14 drinks per week);
- excessive consumption of tea, coffee, chocolate, and/or other xanthine-containing food or beverages;
- positive HIV or HCV test, and/or a positive HBsAg test;
- received blood or plasma derivatives in the year preceding the initiation of the study;
- plasma donation in the 7 days preceding the initiation of the study and blood donation (to the Red Cross or Hema-Quebec) in the 56 days preceding the initiation of the study or intention to make a blood or plasma donation during the study or within the 45 days following the study completion;
- drug treatment during the two weeks preceding the study;
- drug treatment that could lead to induction of hepatic microsomal enzymes (e.g., carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin) within 3 months of the study start;
- subject who had participated in another clinical study of any kind (drug or device) in the month immediately prior to the start of this study;
- subject who, in the judgement of the Investigator, was likely to be non-compliant or uncooperative during the study.

Integrated Clinical and Statistical Report Project No. SKYFEN101-C1-001/ 30364
Comparative Bioavailability of IDD-P™ Fenofibrate Product (tfl1) 160 mg Tablet Administered Under Different Food Conditions with Micronized Fenofibrate 200 mg Capsule Taken Under Low-fat Fed Conditions

<p>Test Product (name (food condition), dose, lot/batch number, expiry/reassay date, administration):</p> <p>IDD-P™ fenofibrate (low-fat fed conditions), SkyePharma Inc., U.S.A.; lot/batch number: H904; reassay date: October 2004; administered as a 1 x 160 mg tablet (Treatment A).</p> <p>IDD-P™ fenofibrate (high-fat fed conditions), SkyePharma Inc., U.S.A.; lot/batch number: H904; reassay date: October 2004; administered as a 1 x 160 mg tablet (Treatment B).</p> <p>IDD-P™ fenofibrate (fasting conditions), SkyePharma Inc., U.S.A.; lot/batch number: H904; reassay date: October 2004; administered as a 1 x 160 mg tablet (Treatment C).</p>
<p>Reference Product (name (food condition), dose, lot/batch number, expiry/reassay date, administration):</p> <p>Lypanthyl® 200M, fenofibrate (micronized) 200 mg capsule, Laboratoires Fournier S.A., France, Lot number: 76769; expiry date: Sep 2006 (also referred to as Tricor, micronized 200 mg in the U.S.A.; Treatment D)</p>
<p>Duration of Treatment:</p> <p>Subjects were given either IDD-P™ fenofibrate 1 x 160 mg tablet under fasting, low-fat fed, or high-fat fed conditions or Fenofibrate capsule 200 mg, reference listed drug 1 x 200 mg capsule under low-fat fed conditions. Subjects were confined to the clinical facility from early evening on the day prior to dosing, until after the 24.0-hour post-dose blood draw in each period. Clinical procedures (return visits to the clinical facility) extended until approximately 72.0 hours post-dose.</p>
<p>Criteria for Evaluation:</p> <p>Pharmacokinetics/Bioavailability:</p> <p>The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-4}, $AUC_{0-\infty}$, C_{max}, % extrapolated, t_{max}, k_{el}, $t_{1/2}$, and F_{rel}.</p> <p>Primary parameters: AUC_{0-4}, $AUC_{0-\infty}$ and C_{max}.</p> <p>Secondary parameters: % extrapolated, t_{max}, k_{el}, $t_{1/2}$ and F_{rel}.</p> <p>Safety:</p> <p>Vital signs (respiratory rate and oral temperature; blood pressure and pulse rate, after having been seated for at least 3 minutes) were performed for each subject during the evening prior to drug administration in Periods 1, 2, 3, and 4.</p> <p>Throughout the study, subjects were monitored for adverse events. At the times of admission, subjects were asked a standard probe question concerning the onset of a new illness since the last visit, and at the time of discharge, each subject was asked how he was feeling.</p> <p>Laboratory tests (hematology, biochemistry, and urinalysis) and vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature) were performed between 4 and 9 days after the last blood draw of the last period. Symptom-targeted physical examinations were also to be performed between 4 and 9 days after the last blood draw of the last period, if necessary.</p>

Statistical Methods:

Descriptive statistics with means, standard deviations, coefficients of variations, medians, interquartile ranges and range (min.) and (max.). ANOVA on ln-transformed AUC_{0-12} , $AUC_{0-\infty}$ and C_{max} and untransformed t_{max} , k_{el} and $t_{1/2}$ at the alpha level of 0.05. Ratio of arithmetic means, ratio of geometric least-squares means and 90% geometric confidence interval around the ratio for ln-transformed AUC_{0-12} , $AUC_{0-\infty}$ and C_{max} for the following comparisons (A/D, B/D, C/D, B/C, B/A and A/C). Analyses are discussed in terms of the bioequivalence limits of 80.00 % to 125.00 %.

Pharmacokinetic/Bioavailability Results:

- Through the study there were no major significant protocol deviations to confound the pharmacokinetics and bioavailability analyses. Seventeen (17) subjects were considered to have completed the clinical portion. However, subject No. 15 was not included in pharmacokinetic analysis since he was not dosed on the correct food conditions for Period 4 (administration under fasting conditions instead of given with high-fat meal). Therefore, data from the remaining 16 subjects were used for the pharmacokinetic analysis since at least 16 subjects were necessary as per the protocol.
- Ratios (A/D) of least-squares means for AUC_{0-12} , $AUC_{0-\infty}$, and C_{max} were 108.03%, 96.96% and 132.08%, respectively, demonstrating a comparable extent of absorption and a slightly higher rate of absorption for IDD-PTM fenofibrate tablet 160 mg given with a low-fat meal (A) than for Fenofibrate capsule 200 mg, reference listed drug given with a low-fat meal (D).
- Ratios (C/D) of least-squares means for AUC_{0-12} , $AUC_{0-\infty}$, and C_{max} were 94.56%, 87.77% and 85.26%, respectively, demonstrating a comparable rate and extent of absorption for IDD-PTM fenofibrate tablet 160 mg given under fasting conditions (C) than for Fenofibrate capsule 200 mg, reference listed drug given with a low-fat meal (D).
- Ratios (B/C) of least-squares means for AUC_{0-12} , $AUC_{0-\infty}$, and C_{max} were 119.46%, 113.88% and 151.49%, respectively, demonstrating a comparable extent of absorption and a higher rate of absorption for IDD-PTM fenofibrate tablet 160 mg given with a high-fat meal (B) than under fasting condition (C).
- Ratios (B/A) of least-squares means for AUC_{0-12} , $AUC_{0-\infty}$, and C_{max} were 104.56%, 103.08% and 97.79%, respectively, demonstrating comparable rate and extent of absorption for IDD-PTM fenofibrate tablet 160 mg given with a high-fat meal (B) than with a low-fat meal (A).
- Ratios (A/C) of least-squares means for AUC_{0-12} , $AUC_{0-\infty}$, and C_{max} were 114.25%, 110.48% and 154.91%, respectively, demonstrating a comparable extent of absorption and a higher rate of absorption for IDD-PTM fenofibrate tablet 160 mg given with a low-fat meal (A) than for IDD-PTM fenofibrate tablet 160 mg under fasting conditions (C).

- ANOVA detected a statistically significant difference between treatments for In-transformed AUC_{0-24} and C_{max} and for untransformed t_{max} , k_{el} and $t_{1/2}$ but not for In-transformed AUC_{0-24} .

Safety Results:

The Investigator judged the reported protocol deviations unlikely to have affected the results or the conclusions of the study.

Physical examinations, vital signs, ECGs, and laboratory tests were performed at the times specified in the protocol. Clinically significant abnormal post-study laboratory results were obtained for 2 subjects: hyperglycemia. All other post-study laboratory test results and final vital signs measurements were within normal limits or were judged to be not clinically significant by a Medical Sub-Investigator.

Alcohol breath tests and urine drug screens were performed for each subject at the times specified in the protocol. All tests yielded negative results for all subjects, with the exception of subject No. 05's urine drug screen test, which yielded a positive result for cocaine at the time of admission in Period 2.

A total of 31 adverse events occurred during the study: 2 adverse events occurred prior to Period 1 dosing and 29 occurred post-dose of Period 1, 2, 3, or 4. The relationship to the study medication of the 29 post-dose adverse events can be broken down as follows: 6 adverse events were judged "possible", 6 were judged "remote", and 17 were judged "unrelated". The pre-dose adverse event was assessed as "unrelated" to the study medication. The severity at onset was mild for 21 adverse events and 5 were moderate. The severity of the remaining 3 adverse events was not graded, as these events were associated with clinically significant post-study laboratory results and an abnormal vital signs measurement. No serious, significant, or severe adverse events were reported.

The reported post-dose adverse events are summarized as follows:

Deaths:	None
Discontinuation from AEs:	None
Serious or severe AEs:	None
Probable-drug-related AEs:	None
Possible-drug-related AEs:	Rash Macula Papular (1), Cough increase (1), Diarrhea (1), Headache (1), Abdominal pain (1), Dyspepsia (1)
Remote-drug-related AEs:	Hyperglycemia (2), Pain chest (1), Insomnia (1), Pharyngitis (1), Vasodilation (1)
Unrelated AEs:	Headache (4), Pain (2), Dizziness (2), Rhinitis (2), Hypertension (1), Nausea (1), Accidental injury (1), Rash Macula Papular (1), Pain back (1), Pain injection site (1), Paresthesia (1)

Summary Conclusions:

Pharmacokinetic/Bioavailability:

Based on the 90% geometric confidence intervals of AUC_{0-12} , $AUC_{0-\infty}$ and C_{max} and the 80.00% to 125.00% range, it can be concluded that IDD-PTM fenofibrate tablet 160 mg when administered under low-fat conditions (Treatment A) has a comparable extent of absorption and essentially comparable (slightly higher) rate of absorption as the reference product (Fenofibrate capsule 200 mg, reference listed drug) given under low-fat conditions (Treatment D). When administered under fasting conditions, IDD-PTM fenofibrate tablet 160 mg (Treatment C) has a comparable extent and rate of absorption as the reference product (Fenofibrate capsule 200 mg, reference listed drug) given under low-fat conditions (Treatment D). Furthermore, there is no effect of food or fat content on the extent of absorption of IDD-PTM fenofibrate. Also, the rate of absorption of IDD-PTM fenofibrate tablet 160 mg is not influenced by the fat content of the test meal administered but is increased when taken with food.

Safety:

All study treatments were well tolerated.

Transfer of Obligations:

No obligations were transferred. SkyePharma Inc. retains all obligations.

Contract research organizations assisted SkyePharma Inc. with the following:

- Clinical site activities: [REDACTED]
 - Ethics committee submissions
 - Study documentation (SkyePharma Inc. prepared the protocol)
 - Study conduct
 - Clinical study report
- Analytical site activities: [REDACTED]
 - Analytical assays
 - Statistical analyses
 - Analytical report

Financial Disclosure:

As per forms FDA 3454 and FDA 3455, there were no disclosable financial arrangements or interests between the study sponsor (SkyePharma Inc.) and clinical study site personnel of [REDACTED] whereby the value of compensation to [REDACTED] could be influenced by the outcome of the study.

Table 1. SKYFEN101-C1-001. Summary of Pharmacokinetic Parameters for IDD-P™ Fenofibrate Tablet 160 mg (low-fat meal) (A), IDD-P™ Fenofibrate Tablet 160 mg (high-fat meal) (B), IDD-P™ Fenofibrate Tablet 160 mg (fasting) (C) and Fenofibrate Capsule 200 mg, Reference Listed Drug (low-fat meal) (D).

Parameters	IDD-P™ fenofibrate tablet 160 mg (A) (low-fat meal)			IDD-P™ fenofibrate tablet 160 mg (B) (high-fat meal)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC ₀₋₄ (ng·h/mL)	150985.37	64057.34	42.43	157334.65	65284.01	41.49
AUC _{0-∞} (ng·h/mL)	166967.16	82212.14	49.24	170504.78	78757.24	46.19
C _{max} (ng/mL)	10554.66	1880.19	17.81	10380.90	2100.10	20.23
% extrapolated (%)	7.28	6.75	92.80	6.27	4.47	71.30
t _{max} (h)	3.06	1.18	38.58	3.63	1.15	31.65
t _{max} * (h)	2.50	2.00	-	3.00	1.25	-
k _{el} (h ⁻¹)	0.0400	0.0123	30.79	0.0424	0.0144	34.02
t _{1/2} (h)	18.83	5.58	29.63	18.06	5.67	31.38
F _{rel} (vs A) (%)	-	-	-	103.01	9.17	8.90
F _{rel} (vs C) (%)	110.53	9.14	8.27	113.82	13.46	11.82
F _{rel} (vs D) (%)	98.31	16.29	16.57	101.26	19.31	19.07

Parameters	IDD-P™ fenofibrate tablet 160 mg (C) (fasting)			Fenofibrate capsule 200 mg, reference listed drug (D) (low-fat meal)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC ₀₋₄ (ng·h/mL)	131350.91	55970.61	42.61	140104.47	59652.38	42.58
AUC _{0-∞} (ng·h/mL)	151367.18	76147.47	50.31	172435.85	83518.68	48.43
C _{max} (ng/mL)	6932.83	2596.83	37.46	8083.95	2187.62	27.06
% extrapolated (%)	10.71	7.07	65.94	14.18	18.34	129.35
t _{max} (h)	3.44	0.73	21.18	4.56	1.21	26.51
t _{max} * (h)	4.00	1.00	-	5.00	1.00	-
k _{el} (h ⁻¹)	0.0337	0.0115	34.22	0.0372	0.0157	42.15
t _{1/2} (h)	22.71	7.15	31.50	22.77	11.79	51.77
F _{rel} (vs D) (%)	89.23	14.95	16.76	-	-	-

* For t_{max}, median and interquartile range are also presented.

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Integrated Clinical and Statistical Report Project No. SKYFEN101-C1-001/ 30364
 Comparative Bioavailability of IDD-PTM Fenofibrate Product (t11) 160 mg Tablet Administered Under Different Food Conditions with Micronized Fenofibrate 200 mg Capsule Taken Under Low-fat Fed Conditions

Table 2. SKYFEN101-C1-001. Summary of Treatment Comparisons for IDD-PTM Fenofibrate Tablet 160 mg (low-fat meal) (A), IDD-PTM Fenofibrate Tablet 160 mg (high-fat meal) (B), IDD-PTM Fenofibrate Tablet 160 mg (fasting) (C) and Fenofibrate Capsule 200 mg, Reference Listed Drug (low-fat meal) (D).

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of Arithmetic Means ¹	Ratio of LS Means ²	90% Confidence Interval ³		Intra-Subject CV
				Lower	Upper	
AUC ₀₋₄	IDD-PTM fenofibrate tablet 160 mg (low-fat meal) (A) vs fenofibrate capsule 200 mg, reference listed drug (low-fat meal) (D)	107.77%	108.03%	96.55%	120.88%	18.92%
	IDD-PTM fenofibrate tablet 160 mg (high-fat meal) (B) vs fenofibrate capsule 200 mg, reference listed drug (low-fat meal) (D)	112.30%	112.96%	101.00%	126.34%	
	IDD-PTM fenofibrate tablet 160 mg (fasting) (C) vs fenofibrate capsule 200 mg, reference listed drug (low-fat meal) (D)	93.75%	94.56%	84.55%	105.76%	
	IDD-PTM fenofibrate tablet 160 mg (high-fat meal) (B) vs IDD-PTM fenofibrate tablet 160 mg (fasting) (C)	119.78%	119.46%	106.76%	133.67%	
	IDD-PTM fenofibrate tablet 160 mg (high-fat meal) (B) vs IDD-PTM fenofibrate tablet 160 mg (low-fat meal) (A)	104.21%	104.56%	93.49%	116.95%	
	IDD-PTM fenofibrate tablet 160 mg (low-fat meal) (A) vs IDD-PTM fenofibrate tablet 160 mg (fasting) (C)	114.95%	114.25%	102.15%	127.78%	
AUC ₀₋₈	IDD-PTM fenofibrate tablet 160 mg (low-fat meal) (A) vs fenofibrate capsule 200 mg, reference listed drug (low-fat meal) (D)	96.83%	96.96%	91.55%	102.70%	9.61%
	IDD-PTM fenofibrate tablet 160 mg (high-fat meal) (B) vs fenofibrate capsule 200 mg, reference listed drug (low-fat meal) (D)	98.88%	99.95%	94.39%	105.84%	
	IDD-PTM fenofibrate tablet 160 mg (fasting) (C) vs fenofibrate capsule 200 mg, reference listed drug (low-fat meal) (D)	87.78%	87.77%	82.88%	92.94%	
	IDD-PTM fenofibrate tablet 160 mg (high-fat meal) (B) vs IDD-PTM fenofibrate tablet 160 mg (fasting) (C)	112.64%	113.88%	107.52%	120.62%	
	IDD-PTM fenofibrate tablet 160 mg (high-fat meal) (B) vs IDD-PTM fenofibrate tablet 160 mg (low-fat meal) (A)	102.12%	103.08%	97.35%	109.15%	
	IDD-PTM fenofibrate tablet 160 mg (low-fat meal) (A) vs IDD-PTM fenofibrate tablet 160 mg (fasting) (C)	110.31%	110.48%	104.33%	116.99%	
C _{max}	IDD-PTM fenofibrate tablet 160 mg (low-fat meal) (A) vs fenofibrate capsule 200 mg, reference listed drug (low-fat meal) (D)	130.56%	132.08%	116.62%	149.58%	20.99%
	IDD-PTM fenofibrate tablet 160 mg (high-fat meal) (B) vs fenofibrate capsule 200 mg, reference listed drug (low-fat meal) (D)	128.41%	129.16%	114.10%	146.21%	
	IDD-PTM fenofibrate tablet 160 mg (fasting) (C) vs fenofibrate capsule 200 mg, reference listed drug (low-fat meal) (D)	85.76%	85.26%	75.32%	96.51%	
	IDD-PTM fenofibrate tablet 160 mg (high-fat meal) (B) vs IDD-PTM fenofibrate tablet 160 mg (fasting) (C)	149.74%	151.49%	133.76%	171.57%	
	IDD-PTM fenofibrate tablet 160 mg (high-fat meal) (B) vs IDD-PTM fenofibrate tablet 160 mg (low-fat meal) (A)	98.35%	97.79%	86.39%	110.70%	
	IDD-PTM fenofibrate tablet 160 mg (low-fat meal) (A) vs IDD-PTM fenofibrate tablet 160 mg (fasting) (C)	152.24%	154.91%	136.85%	175.36%	

¹ Calculated using arithmetic means (untransformed data).
² Calculated using least-squares means (ln-transformed data).
³ 90% Geometric confidence interval based on ln-transformed data.

Figure 1 : Fenofibric Acid Mean Concentration - Time profile; N = 16

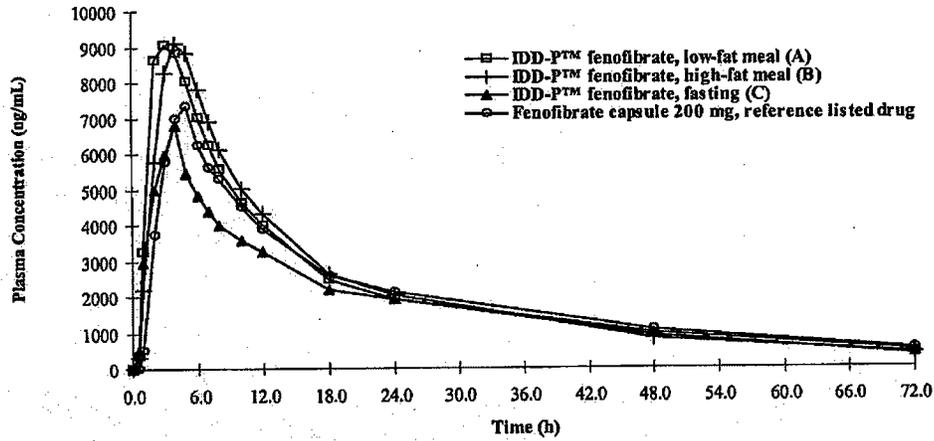
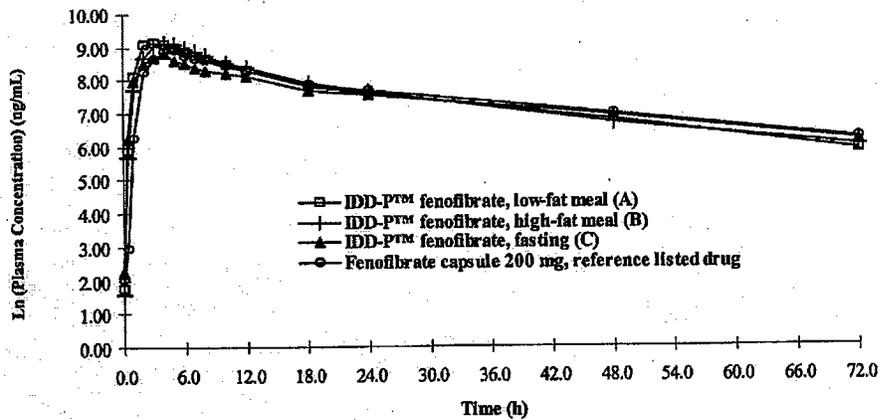


Figure 2: Fenofibric Acid Ln (Mean Concentration) - Time profile; N = 16



4.2 Letter from Fournier Laboratoires

LABORATOIRES

FOURNIER

To whom it may concern

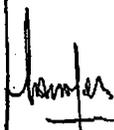
We confirm that the two products Lipanthyl 200M (batch 66467) and Tricor™ 200 mg capsules are:

- identical in term of qualitative and quantitative composition (at the exception of the logo printing on the capsule shell),
- manufactured with the same manufacturing process, equipment and adhere to the same in process controls.

Lipanthyl 200M has been tested in accordance with methodologies defined in the US NDA for Tricor 200 mg and found compliant to all specifications.

Capsules packaged in blisters benefit from the same stability profile than those packaged in  bottles.

Authorized signature :



Xavier Marc SALANÇON
Pharmaceutical Development Fenofibrate Director

Done at Garches, on the 12th April 2002.

CORRESPONDANCE : 153, RUE DE BUZENVAL - 92380 GARCHES - TEL (33) 01 47 10 88 00 - FAX (33) 01 47 10 89 11
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/s/

Wei Qiu
11/29/04 03:27:28 PM
BIOPHARMACEUTICS

Hae-Young Ahn
12/2/04 01:15:11 PM
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-350	Submission Date(s): 22 June 2001, 26 Oct 2001, 28 Dec 2001, 07 Jan. 2002
Relevant IND(s)	60,743
Brand Name	IDD-P™ fenofibrate
Generic Name	fenofibrate
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE II
ORM division	Metabolic and Endocrine Drug Products
Sponsor	RTP Pharma Inc.
Submission Type	Original NDA
Formulation; Strength(s)	Tablet; 160 mg, 50 mg
Indication	Hypertriglyceridemia (Fredrickson Types IV and V)

1 Executive Summary

RTP Pharma Inc. submitted an NDA 21-350 for Insoluble Drug Delivery-Microparticle (IDD-P™) fenofibrate tablets for the treatment of hyperlipidemia under Section 505(b)(2).

Fenofibrate is a lipid-regulating agent that reduces plasma levels of TC and triglycerides (TG) in healthy subjects and in patients with hyperlipidemia. The mechanism of action of fenofibrate is complex and not completely understood. The major effect of fenofibrate is to increase the activity of lipoprotein lipase (LPL), which promotes the lipolysis of very low density lipoprotein (VLDL) and consequently lowers plasma TG levels. Fenofibrate also inhibits hepatic synthesis of fatty acids and triglycerides and inhibits the release of fatty acids from adipose tissue. These actions lead to decreased VLDL synthesis and production of smaller VLDL particles, which in turn favors the formation of more rapidly catabolized low-density lipoprotein (LDL). The mechanism of action of fenofibrate at the molecular level has recently been elucidated and involves the nuclear peroxisome proliferator-activated receptors alpha (PPAR α). PPAR α belongs to the nuclear steroid hormone receptor gene superfamily and has the potential to control the expression of genes involved in intracellular and extracellular lipid metabolism.

IDD-P™ fenofibrate is a new formulation of fenofibrate (fenofibrate tablets, microparticle) designed to decrease the effect of food on drug absorption and to improve the bioavailability of fenofibrate. The U.S.-approved reference listed drugs (RLD) are Tricor™ micronized fenofibrate capsule 200 mg, NDA 19-304 and Tricor™ tablet 160 mg, NDA 21-203. With micronized fenofibrate (Tricor™ capsule and tablet), the absorption is increased by approximately 35% under fed condition compared to fasting conditions. Therefore, for both Tricor™ capsule and tablet, it is recommended to be given with meals.

The Human Pharmacokinetic (PK) and BA study report/data and full chemistry data for IDD-P™ fenofibrate were submitted in this NDA as well as summaries of clinical and nonclinical

information from the marketed product and literature. No clinical trial was conducted with this product.

Section 6 included one pivotal (**FEN100-C05**) and one pilot (FEN100-C03 Part 1) food effect studies, two pivotal (**FEN100-C06 and FEN100-C07**) and two pilot (FEN100-C03 Part 2 and FEN100-C04A) comparative bioavailability studies, one dosage form equivalence study (**FEN100-C12**), one BA study of different IDD-P™ dosage forms (FEN100-C08), and two exploratory studies (FEN100-C10, and FEN100-C11).

Since the sponsor is not seeking approval of formulations other than tablet, the study with other formulations (FEN100-C08) is not included in this review. In addition, since no IDD-P™ products were involved in the two exploratory studies (FEN100-C10 and FEN100-C11), these studies are not included in this review.

The studies showed that the extent of absorption of IDD-P™ fenofibrate tablet was not influenced by food, however, the rate of absorption was increased 60% by food. The rate and extent of absorption of IDD-P™ fenofibrate tablet and Tricor™ micronized fenofibrate capsule were bioequivalent when administered following a low-fat meal.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-350 submitted on 22 June 2001, 26 Oct 2001, 28 Dec 2001, 07 Jan. 2002 and finds it acceptable except the dissolution method and specifications. The following dissolution method and specifications are recommended. However, if the NDA is not approved based on the chemistry deficiencies, a DSI inspection for FEN100-C05 and FEN100-C06 would be requested. If the NDA is approved, a DSI inspection should not hold the approval of the NDA. Recommendation, comments, and labeling comments should be conveyed to the sponsor as appropriate.

Dissolution Method:

Apparatus Type: USP apparatus 2
Speed of Rotation: 50 rpm
Medium: 900 mL sodium lauryl sulfate (SLS), 37°C
Volume: 900 mL

Dissolution specifications:

50 mg: not less than (Q) in 30 minutes
160 mg: not less than (Q) in 60 minutes

Wei Qiu, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader _____

FT initialed by Hae-Young Ahn, Ph.D., Team Leader _____

DFS CODE: AP

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3 Summary of CPB Findings

1. Food Effects:

The bioavailability of IDD-P™ fenofibrate tablet 160 mg was examined under fasting, low-fat fed, and high-fat fed conditions. Ratios (fasting/low-fat fed) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 89.71%, 90.04%, and 61.81%, respectively. Ratios (high-fat fed/low-fat fed) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 106.91%, 106.93%, and 99.84%, respectively. Ratios (high-fat fed/fasting) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 119.18%, 118.76%, and 161.51%, respectively.

Based on the 90% geometric confidence interval of AUC_{0-t} and $AUC_{0-\infty}$ that were within the 80% - 125% range, it was concluded that the extent of absorption of IDD-P™ fenofibrate tablet 160 mg was not influenced by food. However, the rate of absorption of IDD-P™ fenofibrate tablet 160 mg C_{max} was increased by 60% when taken with food. The extent and rate of absorption of IDD-P™ were not influenced by fat content.

2. Relative Bioavailability:

Relative bioavailability of IDD-P™ fenofibrate tablet 160 mg compared with Tricor™ micronized fenofibrate capsule 200 mg was examined under both low-fat fed and fasting conditions. The bioavailability of IDD-P™ fenofibrate tablet 160 mg was comparable to that of Tricor™ micronized fenofibrate capsule 200 mg under low-fat fed conditions. In contrast, under fasting conditions, the bioavailability of IDD-P™ fenofibrate tablet 160 mg was higher than that of Tricor™ micronized fenofibrate capsule 200 mg. Bioequivalence under fasting conditions was expected since Tricor™ has significant food effect.

Under low-fat fed conditions, ratios of (IDD-P™ fenofibrate tablet 160 mg / Tricor™ micronized fenofibrate capsule 200 mg) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 94.09%, 93.69%, and 110.73%, respectively. Based on the 90% geometric confidence intervals of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} that were within the 80% - 125% range, it was concluded that the rate and extent of absorption of IDD-P™ fenofibrate tablet 160 mg and Tricor™ micronized fenofibrate capsule 200 mg were equivalent when administered following a low-fat meal.

Under fasting condition, ratios (IDD-P™ fenofibrate tablet 160 mg / Tricor™ micronized fenofibrate capsule 200 mg) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 153.3%, 142.56%, and 288.29%, respectively. Thus, the IDD-P™ fenofibrate tablet 160 mg demonstrated

a higher extent and rate of absorption compared to Tricor™ micronized fenofibrate capsule 200 mg.

3. Dosage Form Equivalence:

The bioavailabilities of three IDD-P™ fenofibrate 50 mg tablets versus one IDD-P™ fenofibrate 160 mg tablet were compared under low-fat fed conditions. Ratios (three 50 mg tablets/one 160 mg tablet) of least-squares means for AUC₀₋₁, AUC_{0-∞}, and C_{max} were 96.53%, 96.23%, and 97.36%, respectively, for uncorrected data, and 102.97%, 102.65%, and 103.85%, respectively, for dose corrected data. Based on the least-squares means ratios and 90% geometric confidence intervals of AUC₀₋₁, AUC_{0-∞}, and C_{max} that were within the 80% - 125% range for both the uncorrected and dose corrected data, it was concluded that the extent and rate of absorption of IDD-P™ fenofibrate were comparable when administered as 1x160 mg tablet or as 3x50 mg tablets under low-fat fed conditions. Therefore, dosage form equivalence between the two strengths was established.

4 QBR

4.1 General Attributes

Q: What are the formulations of the 50 mg and 160 mg strength tablets?

The compositions of IDD-P™ fenofibrate 50 mg and 160 mg tablets are given in **Table 1**. They vary in the proportional weight of the compressed dosage unit. The manufacturing processes for both strengths were same.

Table 1. Composition of the 50 mg and 160 mg IDD-P™ Fenofibrate Tablets

Component	50 mg Tablet	160 mg Tablet
Fenofibrate	50	160
Egg lecithin		
Monobasic sodium phosphate		
Magnesium stearate		
Colloidal silicon dioxide		
Total weight	1	

4.2 General Clinical Pharmacology

Q. Were adverse events observed in the pivotal PK studies?

Clinically significant abnormal post-study laboratory results were obtained for 11 subjects in 4 pivotal PK studies (FEN100-C05, FEN100-C06, FEN100-C07, and FEN100-C12).

In study FEN10-C05, there were three cases of adverse events.

- Subject No. 03 had a high glucose level (12.4 mmol/L) at approximately 11 days after Period 3 drug administration under low-fat fed condition. The test was repeated approximately 12 days later and yielded a normal result (5.0 mmol/L).
- Subject No. 10 had high creatine kinase (536 U/L) at approximately 11 days after Period 3 drug administration under fasting condition. The test was repeated approximately 19 days later and yielded a result that was judged to be not clinically significant (353 U/L).

- Subject No. 24 had white blood cells in urine (11-20/hpf) at approximately 11 days after Period 3 drug administration under fasting condition. The test was repeated approximately 12 days later and yielded a normal result (0-2/hpf).

The AUC_{0-t} values for all these subjects were below the average. The C_{max} value of Subject No. 03 was below the average, while the C_{max} values for Subjects No. 10 and 24 were slightly higher than the average.

In study FEN100-C06, one subject who presented with a low white blood cell (WBC) count at the time of screening ($3.1 \times 10^9/L$), had a further decline of 23% in white blood cells at the time of the post-study procedures ($2.4 \times 10^9/L$). The post-study procedures result was judged to be clinically significant, but, upon repeat testing approximately 39 days later, the white blood cell count had returned to approximately the baseline value ($3.0 \times 10^9/L$), and was judged to be not clinically significant.

The C_{max} and AUC_{0-t} values for this subject were one half of the respective mean values.

In study FEN100-C07, there were 3 cases of adverse events.

- Subject No. 08 and 24 had red blood cells in urine (3-8/hpf) at approximately 4 days after Period 2 drug administration. Both of them had IDD-P™ fenofibrate tablet 160 mg administration at Period 2. The repeat measurement performed on a sample collected approximately 21 to 28 days for them yielded a normal result.
- Low hemoglobin (110 g/L) was observed in Subject No. 19 after Period 2 drug administration with IDD-P™ fenofibrate tablet 160 mg. The repeat measurement performed on a sample collected approximately 28 days later still yielded a clinically significant results (113 g/L).

The C_{max} values of all these subjects were below the average and the AUC_{0-t} values were slightly higher than the average.

In study FEN100-C12, four cases of adverse events were found.

- Subject No. 05 and 11 had protein in urine (0.3 g/L) in approximately 9 days after Period 2 drug administration with one tablet IDD-P™ fenofibrate 160 mg and three tablets IDD-P™ fenofibrate 50 mg, respectively.
- Subject No. 09 had increased blood levels of glucose (9.5 mmol/L), AST (67 U/L), ALT (48 U/L), and creatine kinase (1459 U/L) levels at approximately 9 days after Period 2 drug administration with three tablets IDD-P™ fenofibrate 50 mg.
- Subject No. 17 had increased creatine kinase level (411 U/L) at approximately 9 days after Period drug administration with three tablets IDD-P™ fenofibrate 50 mg. The tests were repeated and yielded normal or not clinically significant results.

The AUC_{0-t} values for Subjects No. 5, 9, and 11 were higher than the average. The AUC_{0-t} value for Subject No. 17 was lower than the average. The C_{max} values for Subjects 5, 11, and 17 were lower than the average. The C_{max} value for Subject No. 09 was higher than the average.

Overall, no definite correlation can be obtained between clinically significant abnormal post-study laboratory results and PK parameters (i.e., AUC_{0-t} or C_{max}).

4.3 General Biopharmaceutics

Q: Do the tablets used in pharmacokinetic studies and the commercial tablets have the same formulation and manufacturing process?

Pharmacokinetic studies used to support this NDA utilized the identical formulation and comparable process conditions to that proposed for the commercial product. The major difference

between commercial products and the products used in the PK studies was the 10-fold scale up. A summary of the batches used in the pharmacokinetic studies is provided in **Table 2**.

Table 2. Summary of Batches Used in Pharmacokinetic Studies

Product	160 mg Tablet	50 mg Tablet
	Batch 116041 Lot #003	Batch 118719 Lot #001
Significant manufacturing difference	Manufactured at [redacted] commercial scale at commercial site/identical [redacted]	No manufacturing change.
Pivotal PK Study	FEN100-C05, FEN100-C06; FEN100-C07, FEN100-C12	FEN100-C12

Q: Were the dissolution method and specification adequately justified?

The dissolution method and two specifications for IDD-P™ fenofibrate 160 mg and 50 mg tablets proposed by the sponsor were found to be unacceptable.

The proposed dissolution method and specifications are as follows:

Apparatus Type: USP apparatus 2
 Speed of Rotation: 50 rpm
 Medium: [redacted] sodium lauryl sulfate (SLS), 37°C
 Volume: 900 mL

Specifications	20 minutes	60 minutes
160 mg	[redacted]	
50 mg	[redacted]	

Additional dissolution data of [redacted] tablets for both strengths (i.e., 50 mg and 160 mg) using three different dissolution media [redacted] were requested.

The dissolution data are provided in **Table 3** and **Figure 1**. The dissolution results showed that the release was complete for both strengths using [redacted] media. For 50 mg tablets, on average, more than [redacted] of the claimed drug dissolved in 30 minutes. The dissolution rate was slower for the 160 mg tablets. [redacted]

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Draft Labeling

Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

Q: This product was designed to have no food effect. Is there any food effect?

Food increased the rate of absorption by 60% but did not affect the extent of absorption of IDD-P™ fenofibrate tablets. The extent and rate of absorption of IDD-P™ fenofibrate tablet were not influenced by fat content.

An open-label, randomized, single-dose, three-way crossover study (FEN100-C05) was conducted in 24 healthy subjects to assess and compare the bioavailability of IDD-P™ fenofibrate tablet 160 mg under fasting (Treatment A), standard low-fat fed (Treatment B), and high-fat fed (Treatment C) conditions. Twenty subjects completed the study. Subjects in treatment A were administered 1 tablet of IDD-P™ fenofibrate 160 mg after a supervised overnight fast of at least 10 hours. Subjects in treatment B and C were administered 1 tablet of IDD-P™ fenofibrate 160 mg after a supervised overnight fast of at least 9.5 hours and subsequently consumed a low-fat meal in treatment B, and high-fat in treatment C. Doses were separated by washout periods of at least 10 days.

AUC_{0-t}, AUC_{0-∞}, C_{max}, % extrapolated, t_{max}, K_{el}, t_{1/2}, and F_{rel} were calculated for fenofibric acid by non-compartmental method. The results are provided in **Table 4**.

Table 4. Summary of Pharmacokinetic Parameters for IDD-P™ Fenofibrate 160 mg Tablet lot #003 Administered under Fasting (Treatment A), Low-fat Fed (Treatment B) and High-fat Fed (Treatment C) Conditions

Parameters	Fasting (A)		Low-fat fed (B)		High-fat fed (C)	
	Mean	SD	Mean	SD	Mean	SD
AUC _{0-t} (ng.h/mL)	132301.14	31194.10	147713.23	35769.60	156731.95	36382.76
AUC _{0-∞} (ng.h/mL)	135032.51	32025.51	150139.43	36238.46	159318.08	36663.31
C _{max} (ng/mL)	7351.51	1943.44	11649.40	2171.75	11760.62	2893.11
% extrapolated	1.99	1.24	1.63	0.93	1.66	0.71
t _{max} (h)	2.82	1.14	2.86	1.13	3.09	1.54
K _{el} (h ⁻¹)	0.0367	0.0078	0.0420	0.0104	0.0423	0.0113
t _{1/2} (h)	19.79	4.74	17.71	5.21	17.52	4.63
F _{rel} (vs low fat) (%)	90.94	12.86	100.0	0.00	107.37	14.14
F _{rel} (vs fasting) (%)	100.00	0.00	112.22	16.92	119.89	20.58

Ratio of geometric least-squares means (Treatment A/Treatment B), (Treatment C/Treatment B), and (Treatment C/Treatment A) and 90% geometric confidence interval around the ratio of ln-transformed AUC_{0-t}, AUC_{0-∞}, and C_{max} were constructed and are summarized in **Table 5**.

Table 5. Summary of Treatment Comparisons for IDD-P™ Fenofibrate 160 mg Tablet Lot #003 When Administered under Fasting (Treatment A), Low-fat Fed (Treatment B), and High-fat fed (Treatment C) Conditions

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of LS Means	90% Confidence Interval
AUC _{0-t}	A vs. B	89.71%	(85.58%, 94.04%)
	C vs. B	106.91%	(101.97%, 112.09%)
	C vs. A	119.18%	(113.68%, 124.95%)
AUC _{0-∞}	A vs. B	90.04%	(85.97%, 94.29%)
	C vs. B	106.93%	(102.09%, 112.00%)
	C vs. A	118.76%	(113.38%, 124.40%)
C _{max}	A vs. B	61.81%	(55.95%, 68.30%)
	C vs. B	99.84%	(90.33%, 110.35%)
	C vs. A	161.51%	(146.13%, 178.51%)

IDD-P™ fenofibrate 160 mg tablet was slightly less bioavailable when given under fasting conditions (Treatment A) compared to the administration following a low-fat meal (Treatment B) and it was slightly more bioavailable following a high-fat meal (Treatment C) than after the administration of a low-fat meal (Treatment B). ANOVA detected a statistically significant difference between treatments for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , and untransformed $t_{1/2}$ and K_{el} . ANOVA also detected a statistically significant gender by treatment interaction for ln-transformed AUC_{0-t} and $AUC_{0-\infty}$.

Point estimate indicated that high-fat meal increased the extent of absorption of IDD-P™ fenofibrate about 19%. However, since the 90% confidence intervals of AUC_{0-t} and $AUC_{0-\infty}$ were within the range of 80 to 125%, it can be concluded that the extent of absorption of IDD-P™ fenofibrate tablet 160 mg is not influenced by food or the fat content of the test meal administered. The rate of absorption of IDD-P™ fenofibrate tablet 160 mg is increased by 60% when taken with food.

Q: What is the relative bioavailability of of IDD-P™ fenofibrate tablet 160 mg to that of Tricor™ micronized fenofibrate capsule 200 mg?

The relative bioavailability of IDD-P™ fenofibrate tablets 160 mg to Tricor™, micronized fenofibrate capsule 200 mg was examined under low-fat meal and fasting conditions. Under low-fat fed condition, the rate and extent of absorption of IDD-P™ fenofibrate tablet 160 mg and Tricor™ micronized fenofibrate 200 mg capsule were comparable. However, as expected, IDD-P™ fenofibrate tablet 160 mg exhibited a higher extent and rate of absorption compared to Tricor™ micronized fenofibrate capsule 200 mg under fasting conditions.

Low-Fat Fed Condition:

An open-label, randomized, two-way crossover study (FEN100-C06) was conducted to assess the bioavailability of IDD-P™ fenofibrate tablet 160 mg relative to that of Tricor™ micronized fenofibrate capsule 200 mg under standard low-fat meal conditions in 28 healthy subjects.

After a overnight fast of at least 9.5 hours and subsequent consumption of the low-fat test meal, subjects were administered IDD-P™ fenofibrate 160 mg tablet (Treatment A) or Tricor™ micronized fenofibrate capsule 200 mg (Treatment B). Serial blood samples were collected prior to drug administration and 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 18.0, 24.0, 48.0, 72.0, 96.0, and 120.0 hours post-dose, in each period. Of the 28 healthy subjects who were dosed, 2 did not complete the study. Subject No. 01 withdrew from the study prior to Period 2 dosing due to a personal reason. Subject No. 08 withdrew from the study prior to Period 2 dosing because of concomitant medications she had taken. Thus, 26 subjects completed the study. The data of the first 24 subjects who completed the study were used for the pharmacokinetic analysis according to study protocol. Doses were separated by washout periods of at least 10 days.

The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , % extrapolated, t_{max} , K_{el} , $t_{1/2}$, and F_{rel} . The pharmacokinetic parameters are summarized in Table 6.

Table 6. Summary of Pharmacokinetic Parameters for IDD-P™ Fenofibrate 160 mg Tablet Lot #003 (Treatment A) and Tricor™ Micronized Fenofibrate 200 mg Capsule (Treatment B) Given under Low-fat Fed Conditions

Parameters	IDD-P™ fenofibrate Tablet 160 mg (Treatment A)		Tricor™ Micronized fenofibrate Capsule 200 mg (Treatment B)	
	Mean	SD	Mean	SD
AUC_{0-t} (ng.h/mL)	137587.71	48203.28	149272.07	58621.21

AUC _{0-∞} (ng.h/mL)	140067.57	49380.22	152599.13	60529.39
C _{max} (ng/mL)	11204.05	2507.73	10401.84	3039.54
% extrapolated (%)	1.76	1.13	2.12	1.22
t _{max} (h)	3.21	1.10	4.75	0.90
K _{el} (h ⁻¹)	0.0507	0.0220	0.0449	0.0177
t _{1/2} (h)	15.72	5.47	17.77	6.51
F _{rel} (%)	94.05	12.36	100.00	0.00

Ratio of geometric least-squares means (Treatment A/Treatment B) and 90% confidence interval around the ratios for ln-transformed AUC_{0-t}, AUC_{0-∞}, and C_{max} were constructed and are provided in **Table 7**.

Table 7. Summary of Treatment Comparisons for IDD-PTM Fenofibrate 160 mg Tablet Lot #003 (Treatment A) versus TricorTM Micronized Fenofibrate 200 mg Capsule (Treatment B) Given under Low-fat Fed Conditions

Statistical Analysis (Treatment A vs. Treatment B)	Ratio of LS Means	90% Geometric Confidence Interval
AUC _{0-t}	94.09%	(89.15%, 99.31%)
AUC _{0-∞}	93.69%	(89.09%, 98.53%)
C _{max}	110.73%	(101.84%, 120.39%)

Ratios (Treatment A/Treatment B) of least-squares means for AUC_{0-t}, AUC_{0-∞}, and C_{max} were 94.09%, 93.69%, and 110.73%, respectively, demonstrating a slightly lower extent of absorption and a slightly higher rate of absorption of IDD-PTM fenofibrate tablet 160 mg (Treatment A) compared to TricorTM micronized fenofibrate capsule 200 mg administered under low-fat fed conditions. Based on the 90% geometric confidence intervals of AUC_{0-t}, AUC_{0-∞}, and C_{max} that were within the 80-125% range, it can be concluded that the rate and extent of absorption of IDD-PTM fenofibrate tablet 160 mg and TricorTM micronized fenofibrate capsule 200 mg are equivalent when administered under low-fat fed condition.

ANOVA detected a statistically significant difference between treatments for ln-transformed AUC_{0-∞}, C_{max}, and untransformed t_{max} and t_{1/2}. ANOVA also detected a statistically significant difference between genders for ln-transformed C_{max}, and a statistically significant treatment by gender interaction for untransformed t_{max}.

The pharmacokinetics results of two pilot studies (FEN100-C03 part II and C04A) are consistent with the observations from the pivotal study FEN100-C06

Study FEN100-C03 Part II compared bioavailability of IDD-PTM fenofibrate tablet 160 mg lot #003 (Treatment C) and TricorTM micronized fenofibrate capsule 200 mg (Treatment D) under low-fat fed conditions. The results showed that ratios (Treatment C/Treatment D) of geometric least-squares means for AUC_{0-t} and AUC_{0-∞} were 106.02% and 105.07%, respectively. Ratio (Treatment C/Treatment D) of geometric least-squares means for C_{max} was 133.74%. It was concluded that bioavailability was comparable between IDD-PTM fenofibrate tablet 160 mg and TricorTM micronized fenofibrate capsule 200 mg under low-fat meal conditions. ANOVA detected a statistically significant difference between treatments for ln-transformed C_{max} and untransformed t_{max}.

Study FEN100-C04A compared bioavailability of IDD-PTM fenofibrate tablet 160 mg lot #001 (Treatment A) and lot #003 (Treatment B) and Lipidil Supra® fenofibrate microcoated formulation tablet 160 mg (Treatment C) with Lipidil Micro® micronized fenofibrate capsule 200 mg (Treatment D) under low-fat fed conditions in healthy subjects. It was shown that ratios (Treatment A/Treatment D) of least-squares means for AUC_{0-t}, AUC_{0-∞}, and C_{max} were 100.44%, 97.25%, and 111.43%, respectively, demonstrating a comparable extent of absorption and slightly higher rate of absorption with IDD-PTM fenofibrate 160 mg tablet compared to micronized

fenofibrate 200 mg capsule administered under low-fat fed conditions. Ratios (Treatment B/Treatment D) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 101.46%, 97.95%, and 119.05%, respectively, demonstrating a comparable extent of absorption and slightly higher rate of absorption with IDD-P™ fenofibrate 160 mg tablet lot #003 compared to Lipidil Micro® micronized fenofibrate 200 mg capsule administered under low-fat fed conditions. ANOVA detected a statistically significant difference between treatments for In-transformed AUC_{0-t} , $AUC_{0-\infty}$, C_{max} and untransformed t_{max} .

Fasting Condition:

An open-label, single dose, randomized, two-way crossover study (FEB100-C07) was conducted to assess the bioavailability of IDD-P™ fenofibrate tablet 160 mg relative to that of Tricor™ micronized fenofibrate capsule 200 mg under fasting conditions in 24 healthy subjects. Subjects were administered 1 tablet of IDD-P™ fenofibrate 160 mg (Treatment B) or 1 capsule of Tricor™, micronized fenofibrate 200 mg (Treatment A) after a supervised overnight fast of at least 10 hours. Serial blood samples were collected over 120 hours. Of the 24 subjects who were dosed, 23 completed the study. The 20 individuals (9 males and 11 females) who had not missed blood draws at critical time points were included in the pharmacokinetic analysis. Doses were separated by washout periods of at least 10 days.

The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , % extrapolated, t_{max} , K_{el} , $t_{1/2}$, and F_{rel} . The pharmacokinetics results are provided in **Table 8**.

Table 8. Summary of Pharmacokinetic Parameters for Tricor™ Micronized Fenofibrate, Capsule 200 mg (Treatment A) and IDD-P™ Fenofibrate, Tablet 160 mg lot #003 (Treatment B) Given under Standard Fasting Conditions.

Parameters	Tricor™ Micronized Fenofibrate 200 mg Capsule (A)		IDD-P™ Fenofibrate 160 mg Tablet (B)	
	Mean	SD	Mean	SD
AUC_{0-t} (ng.h/mL)	103685.51	36922.59	154562.30	34567.83
$AUC_{0-\infty}$ *(ng.h/mL)	120206.66	55916.44	161380.34	36235.15
C_{max} (ng/mL)	3078.58	1821.38	8049.29	2706.09
% extrapolated *(%)	9.41	10.26	2.67	2.33
t_{max} (h)	6.36	6.16	3.00	1.34
K_{el} *(h ⁻¹)	0.0265	0.0105	0.0356	0.0103
$t_{1/2}$ *(h)	33.00	20.44	21.05	6.17
F_{rel} *(%)	--	--	147.41	37.83

* for these parameters, N=19 instead of 20.

Ratio of geometric least-squares means (Treatment B/Treatment A) and 90% geometric confidence interval around the ratio for In-transformed AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were constructed and are provided in **Table 9**. ANOVA incorporating the gender effect was performed on In-transformed AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} and untransformed t_{max} , K_{el} , and $t_{1/2}$ at the alpha level of 0.05.

Table 9. Summary of Treatment Comparisons for Tricor™ Micronized Fenofibrate Capsule 200 mg (Treatment A) and IDD-P™ Fenofibrate Tablet 160 mg Lot #003 (Treatment B) Given under Standard Fasting Conditions

Statistical Analysis (Treatment A vs. Treatment B)	Ratio of LS Means	90% Geometric Confidence Interval
AUC_{0-t}	153.30%	(141.33%, 166.29%)
$AUC_{0-\infty}$ *	142.56%	(127.29%, 159.65%)
C_{max}	288.29%	(248.48%, 334.48%)

* for this parameter, N=19 instead of 20.

Ratios (Treatment B/Treatment A) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 153.30%, 142.56%, and 288.29%, respectively, demonstrating a higher extent and rate of absorption of the IDD-P™ fenofibrate tablet 160 mg (Treatment B) compared to Tricor™ micronized fenofibrate capsule 200 mg (Treatment A). Based on the least-squares means ratios (Treatment B/Treatment A) and 90% geometric confidence intervals of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} that were above the 80%-125% range, it can be concluded that the rate and extent of absorption of IDD-P™ fenofibrate tablet 160 mg are higher than the rate and extent of absorption of Tricor™ micronized fenofibrate capsule 200 mg under fasting conditions. ANOVA detected a statistically significant difference between treatments for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} , and untransformed t_{max} , $t_{1/2}$, and kel .

Q: Was the dosage form equivalence established between three 50 mg tablets and one 160 mg tablet?

Since the extent and rate of absorption of IDD-P™ fenofibrate tablets were comparable when administered as one 160 mg tablet or three 50 mg tablets under low-fat fed conditions, the dosage form equivalence between three 50 mg tablets and one 160 mg tablet was established.

A single dose, randomized, 2-way crossover study (FEN 100-C12) compared the bioavailability of three tablets of IDD-P™ fenofibrate 50 mg versus one tablet of IDD-P™ fenofibrate 160 mg under low-fat fed conditions. Twenty-four healthy (13 males and 11 females) were enrolled in this study. Serial blood samples were collected up to 120 hours post-dose in each period. Doses were separated by washout periods of at least 10 days.

The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , % extrapolated, t_{max} , K_{el} , $t_{1/2}$, and F_{rel} . The pharmacokinetic parameters are summarized in **Table 10**.

Table 10. Summary of Pharmacokinetic Parameters for one IDD-P™ Fenofibrate Tablet 160 mg Lot #003 (Treatment A) and three IDD-P™ Fenofibrate Tablet 50 mg Lot #001 (Treatment B) Given under Low-fat Fed Conditions

Parameters	IDD-P™ Fenofibrate Tablet 1 x 160 mg (A)		IDD-P™ Fenofibrate Tablet 3 x 50 mg (B)	
	Mean	SD	Mean	SD
AUC_{0-t} (ng.h/mL)	159854.20	38356.37	153455.66	35136.89
$AUC_{0-\infty}$ (ng.h/mL)	163053.19	39568.72	156125.97	36311.61
C_{max} (ng/mL)	12149.51	1308.99	11933.90	2462.90
% extrapolated (%)	1.92	0.95	1.63	0.89
t_{max} (h)	3.14	1.32	2.56	0.66
K_{el} (h ⁻¹)	0.0394	0.0106	0.0400	0.0111
$t_{1/2}$ (h)	18.78	4.96	18.68	5.31
F_{rel} (%)	--	--	96.30	6.68

Ratio of geometric least-squares means (Treatment B/Treatment A) and 90% geometric confidence interval around the ratio for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were constructed and provided in **Table 11**. ANOVA incorporating the gender effect performed on ln-transformed AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} and untransformed t_{max} , K_{el} , and $t_{1/2}$ at the alpha level of 0.05.

Table 11. Summary of Treatment Comparisons for One Tablet IDD-P™ Fenofibrate 160 mg Lot #003 (Treatment A) and three Tablets IDD-P™ Fenofibrate 50 mg Lot #001 (Treatment B) Given under Low-fat Fed Conditions

Statistical Analysis (ANOVA)	Treatment Comparisons	Dose Correction	Ratio of LS Means	90% Confidence Interval
AUC _{0-t}	B vs. A	Uncorrected	96.53%	[93.92%, 99.22%]
		Corrected	102.97%	[100.18, 105.83%]
AUC _{0-∞}	B vs. A	Uncorrected	96.23%	[93.76, 98.77%]
		Corrected	102.65%	[100.01%, 105.36%]
C _{max}	B vs. A	Uncorrected	97.36%	[91.29%, 103.84%]
		Corrected	103.85%	[97.37%, 110.77%]

Ratios (Treatment B/Treatment A) of least-squares means for AUC_{0-t}, AUC_{0-∞}, and C_{max} were 96.53%, 96.23%, and 97.36%, respectively, for uncorrected data, and 102.97%, 102.65%, and 103.85%, respectively, for dose corrected data. These results demonstrated a comparable extent and rate of absorption of three tablets IDD-P™ fenofibrate 50 mg (Treatment B) and one tablet IDD-P™ fenofibrate 160 mg (Treatment A) and dosage form equivalence between the two strengths. ANOVA detected a statistically significant difference between treatments for ln-transformed AUC_{0-t} and AUC_{0-∞} and untransformed t_{max}. ANOVA also detected a statistically significant difference between genders for ln-transformed C_{max} and untransformed t_{1/2} and K_{el}.

4.4 Analytical

Q: Is the analytical method adequately validated?

Plasma levels of fenofibric acid was determined using a HPLC method with UV detection. The validation is acceptable. The analytical methods used in the clinical studies are summarized in **Table 12**.

Table 12. Summary of the Analytical Methods

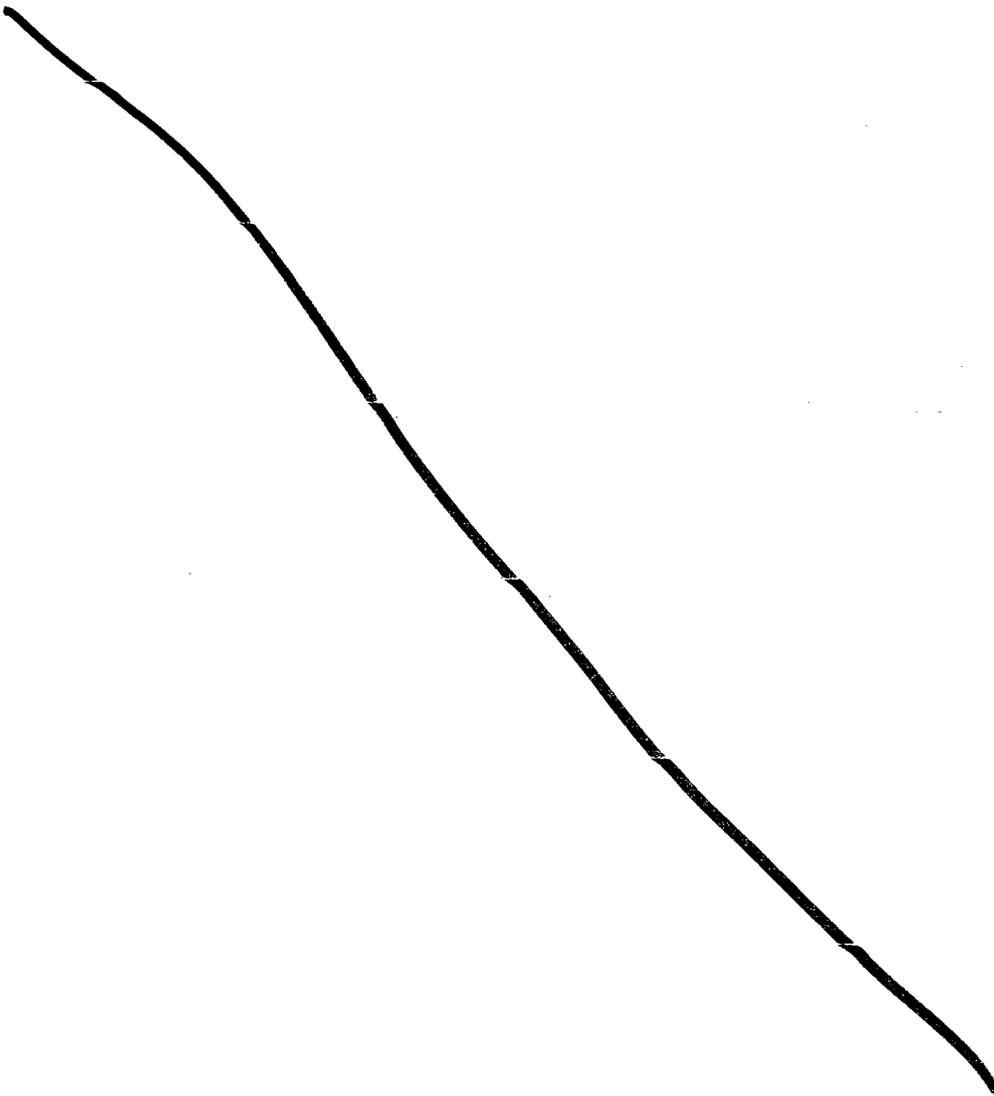
Method Study	ANI 8163.01 (HPLC/UV)		ANI 8232.01 (HPLC/UV)			
	FEN100-C03	FEN100-C04A	FEN100-C05	FEN100-C06	FEN100-C07	FEN100-C12
Sensitivity	50 ng/mL	50 ng/mL	50 ng/mL	50 ng/mL	50 ng/mL	50 ng/mL
Standard curve	50 to 25,000 ng/mL	50 to 25,000 ng/mL	50 to 25,000 ng/mL	50 to 25,000 ng/mL	50 to 25,000 ng/mL	50 to 25,000 ng/mL
QCs	151.59, 8842.75, and 17685.5 ng/mL	149.91, 9125.00, and 18250.00 ng/mL	149.64, 8729.00, and 17458.00 ng/mL	149.64, 8729.00, and 17458.00 ng/mL	150.66, 8788.50, and 17577.00 ng/mL	150.66, 8788.50, and 17577.00 ng/mL
R2	>=0.991	19/20 had >=0.991. one had 0.984	>=0.995	>=0.992	>=0.996	>=0.998
Accuracy (% deviation)	95.51 to 110.06	89.84 to 104.68	101.77 to 102.25	100.04 to 101.27	100.27 to 103.62	102.12 to 103.49
Precision (% RSD)	2.71 to 4.69	3.39 to 5.07	3.66 to 6.89	3.16 to 5.22	4.14 to 4.50	4.39, 19.11*, 9.67

*A high % CV (19.11%) was observed for the QC2 level (nominal concentration of 8788.50 ng/mL). This high value was due to an aberrant value (18475.47 ng/mL) with % nominal of 210.22% observed in an analytical run. Potential samples mix-up between QC2 level and QC3 level was suspected during sample treatment of this analytical run. Calculated statistics without the suspected values gave 3.47% for QC2 and 3.02% for QC3.

5 Comments

1. No food effects can not be claimed because the rate of absorption of IDDP™ fenofibrate tablet 160 mg (C_{max}) was increased by 60% when taken with food.
2. DSI inspection for FEN100-C05 and FEN100-C06 would be requested because of the unusual finding in study FEN100-C05 that the ratio (high fat/fasting) of least-squares mean for AUC_{0-t} was 1.1918 and the upper limit of 90% CI is 1.2495 (not to be sent to the firm).

6 Labeling Comments



27 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Clin Pharm/Bio-2

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*IDD-P™ is a trademark of RTP Pharma Inc.

7.2 Individual Study Reviews

Project No. FEN100-C03/PPL-441/00182

Pilot Study of the Food Effect on the Bioavailability of IDD-PTM Fenofibrate in Healthy Subjects and Comparison with Micronized Fenofibrate Under Low-Fat Fed Conditions

2. STUDY SYNOPSIS

Name of Sponsor/Company: RTP Pharma Inc.	
Name of Finished Product: IDD-PTM fenofibrate	
Name of Active Ingredient: Fenofibrate	
Title of Study: Pilot study of the food effect on the bioavailability of IDD-PTM fenofibrate in healthy subjects and comparison with micronized fenofibrate under low-fat fed conditions	
Investigator(s): Clinical: Principal Investigator: Sub-Investigator(s): Analytical: Principal Investigator:	
Study Centre(s): Clinical: Analytical:	
Publication (reference): None at the date of this report	
Study Period (IRB approval to last scheduled visit): 5 th July 2000 to 27 th September 2000	Phase of Development: Phase I pilot study
Scheduled Dosing Days: Part 1: Period 1 3 rd August 2000 Period 2 13 th August 2000 Part 2: Period 3 23 rd August 2000 Period 4 2 nd & 4 th September 2000	Type of Study: Single dose pharmacokinetics- Part 1: Food-effect Part 2: Comparative Bioavailability

Objectives:

Part 1: To assess the effect of fat from food on the bioavailability of IDD-PTM fenofibrate tablet 160 mg.

Part 2: To compare the bioavailability of IDD-PTM fenofibrate tablet 160 mg and micronized fenofibrate capsule 200 mg, when taken with a low-fat meal.

Methodology:

This was a pilot study with 2 sequential parts. Each part was a single dose, two-treatment, two-period, two-sequence, crossover, open-label, with randomized sequences.

Part 1: IDD-PTM fenofibrate tablet 160 mg, fasting vs. high-fat fed meal conditions (1003 Kcal, 45% fat calories, "50.5 g fat")

Part 2: IDD-PTM fenofibrate tablet 160 mg vs. TricorTM micronized fenofibrate capsule 200 mg, under low-fat fed meal conditions (416 Kcal, 30 % fat calories, "14 g fat")

Dependent on the randomization code, at each study period a single oral dose of drug was administered either fasting or 5 minutes after a test meal. The treatment conditions were as follows:

Treatment Condition A: Fasting (IDD-PTM fenofibrate tablet 160 mg)

Treatment Condition B: High-fat fed meal conditions (IDD-PTM fenofibrate tablet 160 mg)

Treatment Condition C: Low-fat fed meal conditions (IDD-PTM fenofibrate tablet 160 mg)

Treatment Condition D: Low-fat fed meal conditions (micronized fenofibrate capsule 200 mg)

All test meals were eaten over 25 minutes. Washout period between study administrations was a 10-day minimum.

Venous blood samples (8 mL) were withdrawn via an indwelling cannula or by direct venepuncture according to the following time schedule: 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 48, 72 and 96 hours after drug administration. Plasma was separated after collection and frozen aliquots were shipped to the analytical site for measurement of fenofibric acid plasma levels.

Number of Subjects (planned and analyzed):

12 subjects were enrolled into the study.

Part 1: 8 healthy male subjects were entered.

8 subjects dosed successfully completed their respective crossover.

8 subjects were used for the pharmacokinetic and statistical analyses as well as for the safety analyses.

Part 2: 12 healthy male subjects were entered (8 subjects from Part 1 entered Part 2 with 4 additional subjects).
12 subjects successfully completed their respective crossover.
12 subjects were used for the pharmacokinetic and statistical analyses as well as for the safety analyses.

Inclusion and Exclusion Criteria:

Healthy male volunteers aged between 18-55 years old, weighing within $\pm 20\%$ of the Metropolitan Insurance Company scale and deemed "normal" following a comprehensive clinical assessment (including ECG, hematology, blood chemistry, and urinalysis tests) and signing the informed consent form were enrolled.

Subjects were non-smokers and non-tobacco users for at least 3 months, and had negative drug urine screen and alcohol breath test.

Subjects had normal dietary habits and were able to eat study test meals provided.

Subjects were required to have no history of major medical or psychiatric illness or surgery which, in the judgement of the investigator, put the subject at risk, and were not suffering from any acute or chronic systemic disease or disorder.

Subjects had no history of hypersensitivity to fibrate drugs or regular use of sedatives or hypnotics. Subjects had no excessive consumption of tea, coffee, chocolate, and/or xanthine-containing beverages.

Subjects were not taking any prescription medication during the two weeks preceding the study, nor had received within 3 months of starting the study any drug treatment likely to induce hepatic microsomal enzymes.

No blood or plasma donation the 3 months preceding the initiation of the study or intention to make blood or plasma donation during the study or within the 3 months following the study completion.

Test Products (name, dose, lot/batch number, expiry/reassay date, potency, administration):

Part 1: IDD-PTM fenofibrate tablet 160 mg. Lot number: 000615.07.172; Reassay: 08/2000;
Potency: 
One tablet taken orally either fasting or 5 minutes after a high-fat meal.

<p>Part 2: IDD-P™ fenofibrate tablet 160 mg. Lot number: Lot 003; Reassay: 10/2000; Potency: ██████████ Micronized fenofibrate capsule 200 mg (Tricor™). Batch number: 605402E21; Expiry: 01/2002; Potency: ██████████ One tablet taken orally 5 minutes after a low-fat meal.</p>
<p>Duration of Treatment: Each period was a single-dose administration separated by a washout of at least 10 days.</p>
<p>Criteria for Evaluation: <i>Pharmacokinetics/Bioavailability:</i> The following pharmacokinetic parameters were calculated: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, K_{el} and F_{rel}. Primary parameters: AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. Secondary parameters: % extrapolated, t_{max}, K_{el}, $t_{1/2}$ and F_{rel}. Safety: Subjects were routinely questioned at each study visit about the occurrence of any adverse events. Hematology, blood chemistry, and urinalysis test results as well as vital signs were monitored before and after the study treatment period.</p>
<p>Statistical Methods: Descriptive statistics with means, standard deviations, coefficients of variation and range (min.) and (max.). ANOVA for ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} and untransformed t_{max}, K_{el} and $t_{1/2}$ at the alpha level of 0.05. Ratios of geometric least-squares means (B/A) for part 1 and (C/D) for Part 2 and 90% geometric confidence intervals around the ratio for ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.</p>
<p>Pharmacokinetics/Bioavailability Results: Throughout the study there were no significant protocol deviations to confound the pharmacokinetic and bioavailability analyses. Study results were not corrected for drug potency. Part 1: High-fat (B) and fasting (A) bioavailability (See Tables and Figures at end of synopsis) Ratios (B/A) of geometric least-squares means for AUC_{0-t} and $AUC_{0-\infty}$ were 105.56% and 104.99%, respectively, demonstrating that a high-fat meal did not have any significant effect on the extent of absorption of IDD-P™ fenofibrate tablet 160 mg.</p>

Ratio (B/A) of geometric least-squares means for C_{max} was 142.40% demonstrating that a high-fat meal increased the rate of absorption of IDD-PTM fenofibrate tablet 160 mg.

ANOVA detected a statistically significant difference between treatments for ln-transformed C_{max} , as well as for untransformed $t_{1/2}$ and K_{el} .

ANOVA did not detect any statistically significant difference between treatments for ln-transformed AUC_{0-1} , $AUC_{0-\infty}$ and untransformed t_{max} .

Part 2: IDD-PTM fenofibrate tablet 160 mg (C) and micronized fenofibrate capsule 200 mg (D) (See Tables and Figures at end of synopsis)

Ratios (C/D) of geometric least-squares means for AUC_{0-1} and $AUC_{0-\infty}$ were 106.02% and 105.07%, respectively, demonstrating a comparable food effect on the extent of absorption between IDD-PTM fenofibrate tablet 160 mg and micronized fenofibrate capsule 200 mg (Tricor™) administered under low-fat fed conditions.

Ratio (C/D) of geometric least-squares means for C_{max} was 133.74% demonstrating a higher rate of absorption for IDD-PTM fenofibrate tablet 160 mg under low-fat fed conditions compared to micronized fenofibrate capsule 200 mg (Tricor™) administered under low-fat fed conditions.

ANOVA detected a statistically significant difference between treatments for ln-transformed C_{max} and untransformed t_{max} .

ANOVA did not detect any statistically significant difference between treatments for ln-transformed AUC_{0-1} , $AUC_{0-\infty}$ and untransformed $t_{1/2}$ and K_{el} .

Safety Results:

Throughout the study there were no significant protocol deviations to confound the safety analyses.

At the times specified in the protocol, physical examinations, vital signs, ECGs, and laboratory test results (hematology, blood chemistry and urinalysis) were reviewed. During the study no clinically significant changes in these parameters were reported. Final results were either within normal limits or judged not clinically significant by the Medical Investigator. Adverse Events (AE) were mild in severity and no serious or severe AEs were reported. A total of 17 AEs were experienced post-dose by the subjects who completed the study; 5 AEs were unrelated, 6 were remotely related, 3 were possibly related and 3 were probably related to the study drug.

Reported AEs post-dose are summarized as follows:

Deaths: None
Discontinuations from AEs: None
Serious or severe AEs: None
Probably drug-related AEs: Itching (1), headache (2)
Possibly drug-related AEs: Headache (2), nausea (1)
Remotely drug-related AEs: Hematospermia (2), cold sore (1), backache (1), phlebitis (1), headache (1).
Unrelated AEs: Diarrhoea (2), viral throat infection (1), flu-like symptoms (1), mild cold symptoms (1)

Summary Conclusions:

Pharmacokinetic/Bioavailability:

- A high-fat meal did not have any effect on the bioavailability of IDD-PTM fenofibrate tablet 160 mg.
- Bioavailability was comparable between IDD-PTM fenofibrate tablet 160 mg and micronized fenofibrate capsule 200 mg (Tricor™) when administered immediately following a low-fat meal.

Safety:

All study treatments were well tolerated

Transfer of Obligations:

- No obligations were transferred. RTP Pharma retains all obligations.
- Contract research organizations assisted RTP Pharma with the following:
 - Clinical site activities (PPL Address: see above)
 - Ethics committee submissions
 - Study documentation (RTP Pharma prepared the protocol)
 - Study conduct
 - Clinical study report
 - Analytical site activities, [REDACTED] Address: see above)
 - Analytical assays
 - Statistical analyses
 - Analytical report

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Project No. FEN100-C03/PPL-441/00182

Pilot Study of the Food Effect on the Bioavailability of IDD-PTM Fenofibrate in Healthy Subjects and Comparison with Micronized Fenofibrate Under Low-Fat Fed Conditions

Financial Disclosure:

There were no disclosable financial arrangements or interests between the study sponsor (RTP Pharma Inc.) and clinical study site personnel (PPL) and the analytical site personnel [REDACTED] whereby the value of compensation to PPL or [REDACTED] could be influenced by the outcome of the study.

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Project No. FEN100-C03/PPL-441/00182
Pilot Study of the Food Effect on the Bioavailability of IDD-PTM Fenofibrate in Healthy Subjects and Comparison with Micronized Fenofibrate Under Low-Fat Fed Conditions

Table 1.

Parameters	FEN100-C03 Part 1						FEN100-C03 Part 2					
	IDD-PTM fenofibrate fasting (A)			IDD-PTM fenofibrate high-fat fed (B)			IDD-PTM fenofibrate low-fat fed (C)			Micronized fenofibrate low-fat fed (D)		
	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC ₀₋₄ (ng·h/mL)	123563.44	26608.67	21.53	133217.51	39075.48	29.33	139670.95	35080.60	25.12	133934.54	41213.29	30.77
AUC _{0-∞} (ng·h/mL)	126355.62	27273.13	21.58	135288.10	39286.17	29.04	142046.37	35886.94	25.26	137348.22	42280.24	30.78
C _{max} (ng/mL)	7671.68	1897.74	24.74	10726.15	1609.19	15.00	9980.73	1971.33	19.75	7722.53	2386.30	30.90
% extrapolated (%)	2.16	1.37	63.64	1.63	0.79	48.19	1.66	0.67	40.22	2.53	1.45	57.17
t _{max} (h)	2.75	1.75	63.73	3.63	2.26	62.45	3.00	1.35	44.95	5.42	2.24	41.27
K _{el} (h ⁻¹)	0.0424	0.0091	21.36	0.0506	0.0147	29.07	0.0447	0.0095	21.24	0.0435	0.0101	23.33
t _{1/2} (h)	16.99	3.55	20.92	14.48	3.17	21.86	16.03	2.78	17.32	16.63	3.28	19.69
F _{rel} (%)	100.00	0.00	0.00	105.79	14.28	13.50	107.06	23.29	21.76	100.00	0.00	0.00

Table 2.

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of LS Means ¹	Ratio of Arithmetic Means ²	90% Confidence Interval		Intra-subject CV
				Lower	Upper	
AUC ₀₋₄	IDD-PTM fenofibrate high-fat fed (B) vs. IDD-PTM fenofibrate fasting (A)	105.56%	107.81%	94.98 %	117.32 %	10.90%
	IDD-PTM fenofibrate low-fat fed (C) vs. Micronized fenofibrate low-fat fed (D)	106.02%	104.28%	95.01 %	118.30 %	14.90 %
AUC _{0-∞}	IDD-PTM fenofibrate high-fat fed (B) vs. IDD-PTM fenofibrate fasting (A)	104.99%	107.07%	95.38 %	115.58 %	9.91%
	IDD-PTM fenofibrate low-fat fed (C) vs. Micronized fenofibrate low-fat fed (D)	105.07%	103.42%	94.56 %	116.75 %	14.31%
C _{max}	IDD-PTM fenofibrate high-fat fed (B) vs. IDD-PTM fenofibrate fasting (A)	142.40%	139.81%	123.23 %	164.55 %	14.96%
	IDD-PTM fenofibrate low-fat fed (C) vs. Micronized fenofibrate low-fat fed (D)	133.74%	129.24%	114.43 %	156.30 %	21.31%

¹ Calculated using least-squares means (ln-transformed data).

² Calculated using arithmetic means (untransformed data).

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Pilot Study of the Food Effect on the Bioavailability of IDD-PTM Fenofibrate in Healthy Subjects and
Comparison with Micronized Fenofibrate Under Low-Fat Fed Conditions

Figure 1. FEN100-C03 (Part 1): Fenofibric Acid Mean Concentration - Time profile (n = 8).

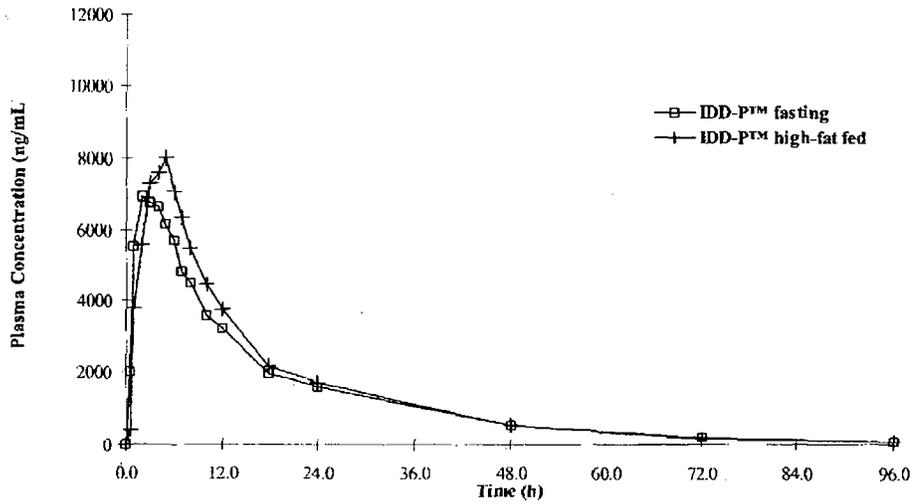


Figure 2. FEN100-C03 (Part 1): Fenofibric Acid Ln (Mean Concentration) - Time profile (n = 8).

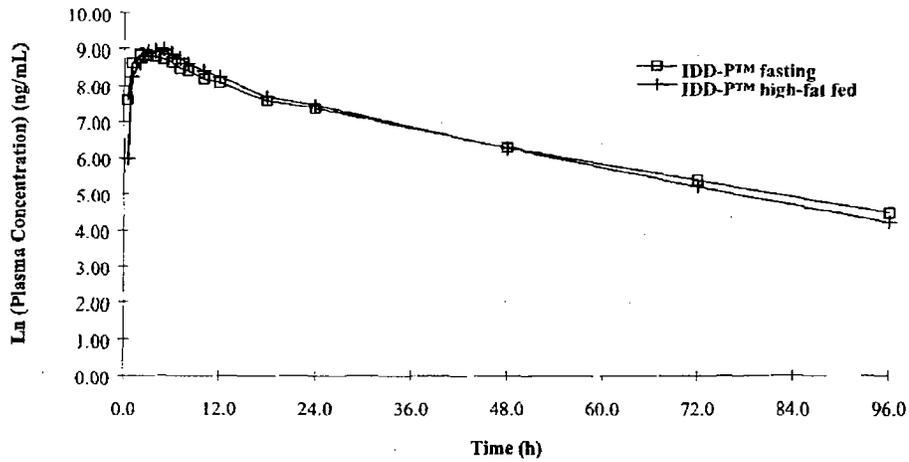


Figure 3. FEN100-C03 (Part 2): Fenofibric Acid Mean Concentration - Time profile (n = 12).

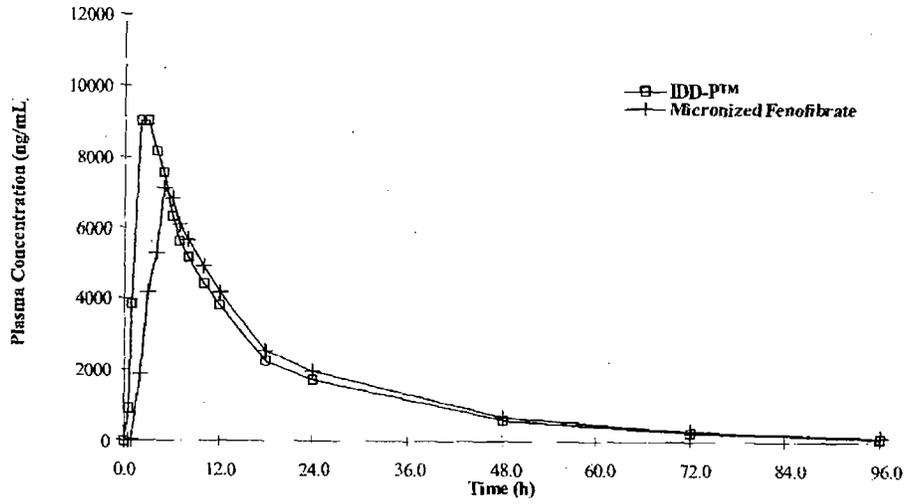
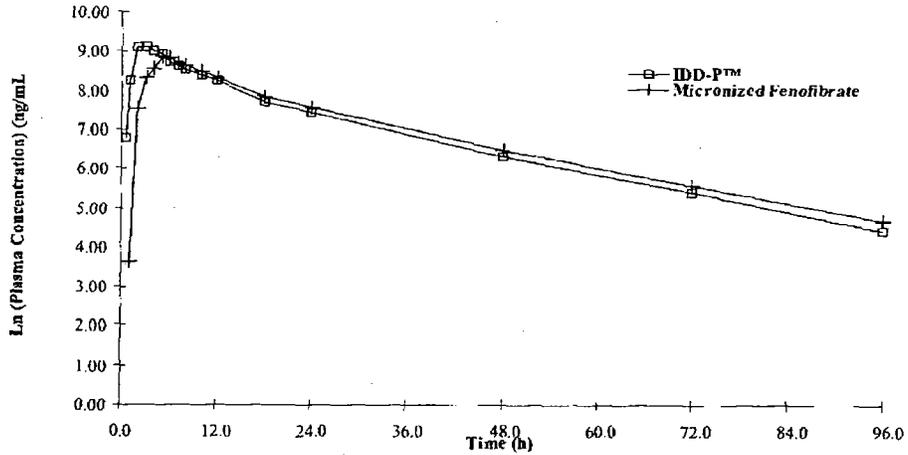


Figure 4. FEN100-C03 (Part 2): Fenofibric Acid Ln (Mean Concentration) - Time profile (n = 12).



1. Title page

Title: Comparative bioavailability of IDD-P™ fenofibrate tablet 160 mg and fenofibrate microcoated formulation tablet 160 mg with micronized fenofibrate capsule 200 mg in healthy subjects

Test drug: IDD-P™ fenofibrate tablet 160 mg (lot #001), IDD-P™ fenofibrate tablet 160 mg (lot #003), Lipidil Supra®, fenofibrate microcoated formulation tablet 160 mg, and Lipidil Micro® micronized fenofibrate capsule 200 mg taken 5 minutes after a low-fat test meal

Indication: This was a single center, open-label, randomized, 4-way crossover study to assess the bioavailability of IDD-P™ fenofibrate tablet 160 mg, from two separate lots, and fenofibrate microcoated formulation tablet 160 mg, relative to that of micronized fenofibrate capsule 200 mg, under low-fat meal conditions. Doses were separated by washout periods of at least 10 days.

Sponsor's name and address: RTP Pharma Inc., 1000 chemin du Golf, Verdun, Quebec, Canada, H3E 1A8
Contact: Dr. Pol-Henri Guivarc'h; tel. (514) 362-9818 ext. 264;
fax (514) 362-1172

Study number(s): _____ - FEN100-C04A _____

Development phase: Phase I, pilot, bioavailability study

Study dosing dates: September 7, 2000 – September 18, 2000 – September 28, 2000 –
October 9, 2000

Study Completion Date: October 26, 2000

Investigator(s): _____

Investigator: . _____

Date: March 2, 2001

Confidentiality statement: This document is strictly confidential. It was developed for RTP Pharma Inc. and should not be disclosed to a third party, with the exception of regulatory agencies and study audit personnel. Reproduction, modification, or adaptation, in part or in total, is strictly forbidden without prior written approval by RTP Pharma Inc.

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Project No. FEN100-C04A / 00183

Comparative Bioavailability of IDD-P™ Fenofibrate Tablet 160 mg and Fenofibrate Microcoated Tablet 160 mg with Micronized Fenofibrate Capsule 200 mg in Healthy Subjects

2. Study Synopsis

Name of Sponsor/Company: RTP Pharma Inc., Canada	
Name of Finished Product: IDD-P™ fenofibrate	
Name of Active Ingredient: Fenofibrate	
Title of Study: Comparative bioavailability of IDD-P™ fenofibrate tablet 160 mg and fenofibrate microcoated formulation tablet 160 mg with micronized fenofibrate capsule 200 mg in healthy subjects	
Investigator(s): Principal Investigator: _____ Sub-Investigator(s): _____	
Study Centre(s): Clinical: _____ Analytical: _____	
Publication (reference): None at the date of this report	
Study Period (IRB approval to last scheduled visit): August 25, 2000, to October 22, 2000	Phase of Development: Phase I pilot study
Scheduled dosing days: Period 1: September 7, 2000 Period 2: September 18, 2000 Period 3: September 28, 2000 Period 4: October 9, 2000	Type of Study: Single dose pharmacokinetics- Comparative bioavailability
Objectives: The objective of this study was to assess the bioavailability of IDD-P™ fenofibrate tablet 160 mg, from two separate lots, and fenofibrate microcoated formulation tablet 160 mg, relative to that of micronized fenofibrate capsule 200 mg, under low-fat meal conditions.	

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Methodology:

This was a single-center, open-label, randomized, four-treatment, four-period, four-sequence crossover pilot study to assess the bioavailability of IDD-P™ fenofibrate tablet 160 mg, from two separate lots, and fenofibrate microcoated formulation tablet 160 mg, relative to that of micronized fenofibrate capsule 200 mg, under low-fat meal conditions. Doses were separated by washout periods of at least 10 days. Sixteen (16) healthy, adult, male non-smokers (for at least 3 months) were enrolled in this study. Subjects were confined from at least 21:00 on the night before dosing until after the 24.0-hour post-dose blood draw, in each period.

Subjects were administered IDD-P™ fenofibrate 160 mg tablet lot #001 (treatment A), IDD-P™ fenofibrate 160 mg tablet lot #003 (treatment B), microcoated fenofibrate 160 mg tablet (treatment C), and micronized fenofibrate 200 mg capsule (treatment D). The drug (one tablet or one capsule) was given after a supervised overnight fast of at least 9.5 hours and subsequent to the consumption of a low-fat test meal (416 Kcal, 30% fat calories, 14 g of fat). All test meals were consumed over an interval of 15 minutes and were completed 5 minutes prior to study drug administration. The washout period between study drug administrations was of at least 10 days.

All blood samples were drawn into blood collection tubes (1 x 7 mL) containing EDTA prior to drug administration and 0.500, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 18.0, 24.0, 48.0, 72.0, and 96.0 hours post-dose, in each period. All blood samples were collected via direct venipuncture.

Blood samples were _____ for 10 minutes at approximately 4°C. Two aliquots of at least 1.2 mL of plasma (when possible) were dispensed into _____ tubes as soon as possible, before being transferred to a -20°C±5°C freezer, pending analysis.

Number of Subjects (planned and analyzed):

Of the 16 healthy, adult, male non-smokers who were dosed, 2 did not complete the study. Subject Nos. 01 and 02 elected to withdraw from the study prior to Period 3 drug administration, due to personal reasons. Thus, 14 subjects completed the study. The data of the first 12 who completed the study were used for pharmacokinetics/bioavailability analysis. Safety analysis and procedures were performed for the 16 subjects who were dosed.

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Inclusion and Exclusion Criteria:

Inclusion Criteria:

- 18 to 55 year old males;
- weight within $\pm 20\%$ of the ideal body weight of the Metropolitan Insurance Company scale;
- deemed "normal" following a comprehensive clinical assessment (detailed medical history, complete physical examination, and ECG) and laboratory investigations (hematology, blood chemistry, urinalysis), the results of which must be within the normal range and/or clinically acceptable for healthy subjects;
- non-smoker, non-tobacco user for at least 3 months;
- negative drug urine screen and alcohol urine or breath test;
- subjects with "normal" dietary habits (i.e., no restrictive regimen) and willing to eat the study test meal;
- informed subjects accepting the study constraints and restrictions and having signed the informed consent.

Exclusion Criteria:

- history of major medical/psychiatric illness or surgery which, in the judgement of the investigator, puts the subject "at risk" or is likely to modify his handling of the study drug;
- suffering from any acute or chronic systemic disease or disorder;
- history of hypersensitivity or intolerance to fibrate drugs or heparin;
- regular use of sedatives, hypnotics, tranquilizers or any other addictive substances;
- signs, symptoms and laboratory test values outside the clinically acceptable "normal range" for healthy subjects;
- history or evidence of acute or chronic alcohol abuse (>14 drinks per week);
- excessive consumption (> 5 cups/day) of tea, coffee, chocolate, and/or other xanthine-containing food or beverages;
- positive HIV or HCV test, and/or a positive HBsAg test;
- received blood or plasma derivatives in the year preceding the initiation of the study;
- blood or plasma donation in the 3 months preceding the initiation of the study or intention to make blood or plasma donation during the study or within the three months following the study completion;
- drug treatment during the two weeks preceding the study;
- drug treatment that could lead to induction of hepatic microsomal enzymes (e.g., carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin) within 3 months of the study start;
- subject who has participated in another clinical study of any kind (drug or device) in the month immediately prior to the start of this study;
- subject who, in the judgment of the investigator, is likely to be non-compliant or uncooperative during the study;
- subject who has forfeited his freedom by administrative or legal award or who is under guardianship;
- subject who cannot be contacted in case of emergency.

Test Products (name, dose, lot/batch number, expiry/reassay date, potency, administration):

IDD-P™ fenofibrate 160 mg tablet, RTP Pharma Inc., Canada; lot number: 001; reassay: 2000/10; potency: [redacted] /tablet; administered as a 1 x 160 mg tablet.

IDD-P™ fenofibrate 160 mg tablet, RTP Pharma Inc., Canada; lot number: 003; reassay: 2000/10; potency: [redacted] /tablet; administered as a 1 x 160 mg tablet.

Lipidil Supra® microcoated fenofibrate 160 mg tablet, Laboratoires Fournier S.A., France (distributed by Fournier Pharma, Inc., Canada); lot number: 62236; expiry: 02/2002; potency: [redacted] /tablet; administered as a 1 x 160 mg tablet.

Lipidil Micro® micronized fenofibrate 200 mg capsule, Laboratoires Fournier S.A., France (distributed by Fournier Pharma, Inc., Canada); lot number: F1351A; expiry: 01/2003; potency: [redacted] /capsule; administered as a 1 x 200 mg capsule.

For all drug administrations, one tablet or capsule was taken orally 5 minutes after a low-fat meal.

Duration of Treatment:

Subjects were given IDD-P™ (fenofibrate; lot #001 [treatment A] or lot #003 [treatment B]), Lipidil Supra® (fenofibrate microcoated formulation; treatment C), or Lipidil Micro® (fenofibrate micronized formulation; treatment D) after a low-fat test meal. Subjects were confined to the clinical facility from at least 21:00 on the night prior to drug administration, until after the 24.0-hour post-dose blood draw, in each period. Clinical procedures (return visits to the clinical facility) extended until approximately 96 hours post-dose.

Criteria for Evaluation:

Pharmacokinetics/Bioavailability:

The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , % extrapolated, t_{max} , K_{el} , $t_{1/2}$, and F_{rel} .

Primary parameters: AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Secondary parameters: % extrapolated, t_{max} , K_{el} , $t_{1/2}$ and F_{rel} .

Safety:

Vitals signs (pulse rate, blood pressure, respiratory rate, and oral temperature) were performed for each subject (seated for at least 3 minutes) during the evening before Periods 1, 2, 3, and 4 drug administration.

On the evening prior to Period 1 dosing, an alcohol breath test and urine drug screen were performed for each subject.

Throughout the study, subjects were monitored for adverse events. At the times of admission, subjects were asked a standard probe question concerning the onset of a new illness since the last visit, and at the time of discharge, each subject was asked how he was feeling.

Laboratory tests (hematology, biochemistry, and urinalysis), physical examinations, and vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature) were performed between 6 and 9 days after the last blood draw of the last period.

Statistical Methods:

Descriptive statistics with mean, standard deviations, coefficients of variation and range (min.) and (max.). ANOVA for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} and untransformed t_{max} , K_{el} and $t_{1/2}$ at the alpha level of 0.05. Ratio of geometric least-squares means (A/D), (B/D) and (C/D) and 90% geometric confidence interval around the ratio for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Pharmacokinetics/Bioavailability Results:

Through the study, there were no significant protocol deviations to confound the pharmacokinetics and bioavailability analyses. Study results were not corrected for drug potency.

- Ratios (A/D) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were 100.44%, 97.25% and 111.43%, respectively, demonstrating a comparable extent of absorption and slightly higher rate of absorption with IDD-PTM fenofibrate 160 mg tablet lot #001 (A) compared to micronized fenofibrate 200 mg capsule (Lipidil Micro[®]) (D) administered under low-fat fed conditions.
- Ratios (B/D) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were 101.46%, 97.95% and 119.05%, respectively, demonstrating a comparable extent of absorption and slightly higher rate of absorption with IDD-PTM fenofibrate 160 mg tablet lot #003 (B) compared to micronized fenofibrate 200 mg capsule (Lipidil Micro[®]) (D) administered under low-fat fed conditions.
- Ratios (C/D) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were 90.47%, 88.80% and 87.18%, respectively, demonstrating a slightly lower extent and rate of absorption with microcoated fenofibrate 160 mg tablet (Lipidil Supra[®]) (C) compared to micronized fenofibrate 200 mg capsule (Lipidil Micro[®]) (D) administered under low-fat fed conditions.
- ANOVA detected a statistically significant difference between treatments for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$, C_{max} and untransformed t_{max} .
- ANOVA did not detect any statistically significant difference between treatments for untransformed $t_{1/2}$ and K_{el} .

Safety Results:

The Principal Investigator judged the reported deviations unlikely to have affected the results of the study.

Physical examinations, vital signs, ECGs, and laboratory tests were performed at the times specified in the protocol. A clinically significant abnormal post-study laboratory result was obtained for one subject (creatinine kinase) but was normal upon retest. All final post-study laboratory test results and vital signs measurements were within normal limits or judged to be not clinically significant by a Medical Sub-Investigator.

Alcohol breath tests and urine drug screens were performed for each subject at the times specified in the protocol. All tests yielded negative results.

Safety Results (cont'd):

Of the 19 post-dose adverse events reported, 6 adverse events were judged unrelated to the study medication, 3 were judged unlikely related, 10 were judged possibly related, and 0 were judged probably related. The severity at onset was mild for 16 adverse events, moderate for 2 adverse events, and recorded as "not applicable" for 1 adverse event (post-study laboratory test result). No serious or severe adverse events were reported.

The reported post-dose adverse events are summarized as follows:

Deaths:	None
Discontinuations from AEs:	None
Serious or severe AEs:	None
Probably drug-related AEs:	None
Possibly drug-related AEs:	Abdominal pain (1), dizziness (1), flatulence (1), headache (2), increase in creatinine kinase (1), pain (1), somnolence (3)
Unlikely drug-related AEs:	Back pain (1), pharyngitis (1), rash (1)
Unrelated AEs:	Asthenia (1), cough (1), dizziness (1), ecchymosis (1), headache (1), rhinitis (1)

Summary Conclusions:

Pharmacokinetic/Bioavailability:

- Bioavailability was comparable between IDD-PTM fenofibrate 160 mg tablet and micronized fenofibrate 200 mg capsule (Lipidil Micro®) when administered immediately following a low-fat meal.
- Bioavailability was comparable between microcoated fenofibrate 160 mg tablet (Lipidil Supra®) and micronized fenofibrate 200 mg capsule (Lipidil Micro®) when administered immediately following a low-fat meal.

Safety:

All study treatments were well tolerated.

Transfer of Obligations:

No obligations were transferred. RTP Pharma retains all obligations.

Contract research organizations assisted RTP Pharma with the following:

- Clinical site activities (██████████ Address: see above)
 - Ethics committee submissions
 - Study documentation (RTP Pharma prepared the protocol)
 - Study conduct
 - Clinical study report
- Analytical site activities (██████████ Address: see above)
 - Analytical assays
 - Statistical analyses
 - Analytical Report

Project No. FEN100-C04A / 00183

Comparative Bioavailability of IDD-PTM Fenofibrate Tablet 160 mg and Fenofibrate Microcoated Tablet 160 mg with Micronized Fenofibrate Capsule 200 mg in Healthy Subjects

Transfer of Obligations (cont'd):

Financial Disclosure:

As per forms FDA 3455 and FDA 3454, there were no disclosable financial arrangements or interests between the study sponsor (RTP Pharma Inc.) and clinical study site personnel of _____ whereby the value of compensation to _____ could be influenced by the outcome of the study.

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Project No. FEN100-C04A / 00183
 Comparative Bioavailability of IDD-PTM Fenofibrate Tablet 160 mg and Fenofibrate Microcoated Tablet 160 mg with Micronized Fenofibrate Capsule 200 mg in Healthy Subjects

Table 1. FEN100-C04A. Summary of Pharmacokinetic Parameters for IDD-PTM Fenofibrate 160 mg Tablet lot #001 (A), IDD-PTM Fenofibrate 160 mg lot #003 Tablet (B), Lipidil Supra[®] Microcoated Fenofibrate 160 mg Tablet (C) and Lipidil Micro[®] Micronized Fenofibrate 200 mg Capsule (D) Given under Low-fat Fed Conditions

Parameters	IDD-PTM fenofibrate (Lot #001) (A)			IDD-PTM fenofibrate (Lot #003) (B)			Microcoated fenofibrate (C)			Micronized fenofibrate (D)		
	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC ₀₋₁ (ng·h/mL)	161743.02	71018.11	43.91	162586.96	74283.26	45.69	148302.44	77871.32	52.51	158149.18	60000.54	37.94
AUC _{0-∞} (ng·h/mL)	173277.94	90800.64	52.40	173839.52	94832.41	54.55	161594.98	97197.64	60.15	176463.20	86818.31	49.20
C _{max} (ng/mL)	9342.42	1902.74	20.37	9982.25	1752.94	17.56	7520.38	2259.62	30.05	8507.68	1812.33	21.30
% extrapolated (%)	4.55	4.54	99.69	4.24	4.59	108.08	5.87	5.29	90.14	7.40	7.25	97.95
t _{max} (h)	3.50	1.00	28.57	3.26	1.13	34.63	3.67	1.32	35.82	4.67	1.22	26.13
K _e (h ⁻¹)	0.0342	0.0077	22.46	0.0354	0.0092	25.83	0.0321	0.0087	27.04	0.0316	0.0078	24.80
t _{1/2} (h)	21.45	6.17	28.75	21.01	6.52	31.02	23.36	7.40	31.66	23.60	7.67	32.50
F _{rel} (%)	97.61	11.02	11.29	97.70	11.88	12.16	88.82	12.35	13.90	100.00	0.00	0.00

Table 2. FEN100-C04A. Summary of Treatment Comparisons for IDD-PTM Fenofibrate 160 mg Tablet lot #001 (A), IDD-PTM Fenofibrate 160 mg lot #003 Tablet (B), and Lipidil Supra[®] Microcoated Fenofibrate 160 mg Tablet (C) versus Lipidil Micro[®] Micronized Fenofibrate 200 mg Capsule (D) Given under Low-fat Fed Conditions

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of LS Means ¹	Ratio of Arithmetic Means ²	90% Confidence Interval		Intra-Subject CV
				Lower	Upper	
AUC ₀₋₁	IDD-PTM fenofibrate (Lot #001) (A) vs Micronized fenofibrate (D)	100.44%	102.27%	94.24%	107.05%	9.16%
	IDD-PTM fenofibrate (Lot #003) (B) vs Micronized fenofibrate (D)	101.46%	102.81%	95.17%	108.17%	
AUC _{0-∞}	Micronized fenofibrate (C) vs Micronized fenofibrate (D)	90.47%	93.77%	84.86%	96.45%	8.98%
	IDD-PTM fenofibrate (Lot #001) (A) vs Micronized fenofibrate (D)	97.25%	98.19%	91.35%	103.53%	
	IDD-PTM fenofibrate (Lot #003) (B) vs Micronized fenofibrate (D)	97.95%	98.51%	91.99%	104.30%	
	Micronized fenofibrate (C) vs Micronized fenofibrate (D)	88.80%	91.57%	93.40%	94.56%	
C _{max}	IDD-PTM fenofibrate (Lot #001) (A) vs Micronized fenofibrate (D)	111.43%	109.81%	97.66%	127.14%	19.08%
	IDD-PTM fenofibrate (Lot #003) (B) vs Micronized fenofibrate (D)	119.05%	117.33%	104.29%	135.91%	
	Micronized fenofibrate (C) vs Micronized fenofibrate (D)	87.18%	88.40%	76.37%	99.52%	

¹ Calculated using least-squares means (ln-transformed data).

² Calculated using arithmetic means (untransformed data).

Figure 1. Fenofibric Acid Mean Concentration - (Time profile; n = 12)

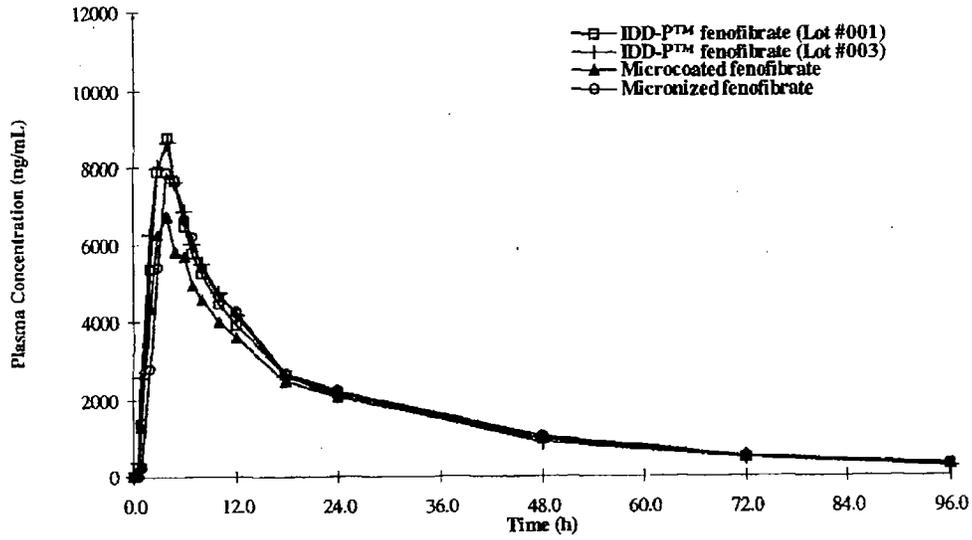
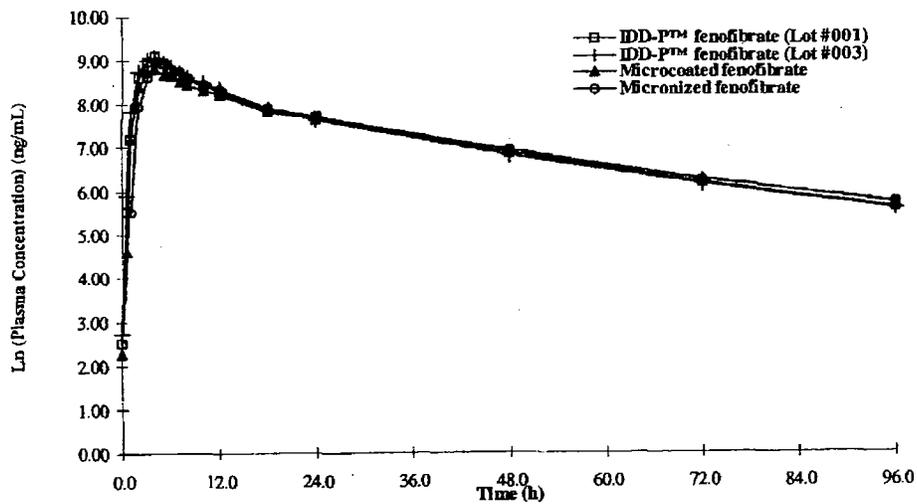


Figure 2. Fenofibric Acid Ln (Mean Concentration)- (Time profile; n = 12)



1. Title page

Title: Comparative bioavailability of IDD-PTM fenofibrate tablet 160 mg under fasting, low-fat fed and high-fat fed conditions in healthy subjects

Test drug: IDD-PTM fenofibrate tablet 160 mg

Indication: This was a single center, open-label, randomized, 3-way crossover study to assess and compare the bioavailability of IDD-PTM fenofibrate tablet 160 mg under fasting, standard (low-fat) fed, and high-fat fed conditions. Doses were separated by washout periods of at least 10 days.

Sponsor's name and address: RTP Pharma Inc., 1000 chemin du Golf, Verdun, Quebec, Canada, H3E 1H4
Contact: Dr. Pol-Henri Guivarc'h; tel. (514) 362-9818 ext. 264;

Study number(s): _____

Development phase: Phase I pharmacokinetic study

Study dosing dates: September 17, 2000 – October 1, 2000 – October 15, 2000
Study Completion Date: November 14, 2000

Investigator(s): _____

Investigator: _____

Date: May 31, 2001

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2. Study Synopsis

Name of Sponsor/Company: RTP Pharma Inc., Canada	
Name of Finished Product: IDD-P™ fenofibrate	
Name of Active Ingredient: Fenofibrate	
Title of Study: Comparative bioavailability of IDD-P™ fenofibrate tablet 160 mg under fasting, low-fat fed and high-fat fed conditions in healthy subjects	
Investigator(s): Principal Investigator: _____ Sub-Investigator(s): _____	
Study Centre(s): Clinical: _____ Analytical: _____	
Publication (reference): None at the date of this report	
Study Period (IRB approval to last scheduled visit): August 31, 2000, to October 29, 2000	Phase of Development: Phase I study
Scheduled dosing days: Period 1: September 17, 2000 Period 2: October 1, 2000 Period 3: October 15, 2000	Type of Study: Single dose pharmacokinetics- Comparative bioavailability
Objectives: The objective of this study was to assess and compare the bioavailability of IDD-P™ fenofibrate tablet 160 mg under fasting, standard (low-fat) fed, and high-fat fed conditions.	

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Methodology:

This was a single-center, open-label, randomized, three-treatment, three-period, six-sequence crossover study to assess and compare the bioavailability of IDD-PTM fenofibrate tablet 160 mg under fasting, standard (low-fat) fed, and high-fat fed conditions. Doses were separated by washout periods of at least 10 days. Twenty-four (24) healthy, adult, non-smokers (for at least 3 months) were enrolled in this study. Subjects were confined from at least 22:00 on the night before dosing until after the 24.0-hour post-dose blood draw in each period.

Subjects in treatment A were administered 1 tablet of IDD-PTM fenofibrate 160 mg after a supervised overnight fast of at least 10 hours. Subjects in treatments B and C were administered 1 tablet of IDD-PTM fenofibrate 160 mg after a supervised overnight fast of at least 9.5 hours and subsequent consumption of a test meal (low-fat [LF] for subjects in treatment B, and high-fat [HF] for subjects in treatment C). These meals were consumed over an interval of 25 minutes and were completed 5 minutes prior to study drug administration.

All blood samples were drawn into blood collection tubes (1 x 7 mL) containing EDTA prior to drug administration and 0.500, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 18.0, 24.0, 48.0, 72.0, 96.0, and 120.0 hours post-dose, in each period. All blood samples were collected via direct venipuncture.

Blood samples were [redacted] for 10 minutes at approximately 4°C. Two aliquots of at least 1.2 mL of plasma (when possible) were dispensed into [redacted] tubes as soon as possible, before being transferred to a -20°C±5 °C freezer, pending analysis.

Number of Subjects (planned and analyzed):

Of the 24 healthy, adult, male (M) and female (F) non-smokers who were dosed, 2 did not complete the study. Subject No. 01 (F) was withdrawn from the study by a Medical Sub-Investigator after Period 1 drug administration, due to adverse events (fainting [unrelated to the study medication] and nausea [possibly related to the study medication]). Subject No. 13 (M) was withdrawn from the study by the Clinical Project Coordinator, due to a positive urine drug screen at the time of Period 2 admission. Thus, 22 subjects (11 males and 11 females) completed the study. The data of all subjects who completed the study were used for the pharmacokinetics/bioavailability analyses. Safety analysis and procedures were performed for the 24 subjects who were dosed.

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Inclusion and Exclusion Criteria:

Inclusion Criteria:

- 18 to 55 years old;
- weight within $\pm 20\%$ of the ideal body weight of the Metropolitan Insurance Company scale;
- deemed "normal" following a comprehensive clinical assessment (detailed medical history, complete physical examination, and ECG) and laboratory investigations (hematology, blood chemistry, urinalysis), the results of which must be within the normal range and/or clinically acceptable for healthy subjects;
- non-smoker, non-tobacco user for at least 3 months;
- negative drug urine screen and alcohol urine or breath test;
- subjects with "normal" dietary habits (i.e., no restrictive regimen) and willing to eat the study test meals;
- informed subjects accepting the study constraints and restrictions and having signed the informed consent.

Exclusion Criteria:

- history of major medical/psychiatric illness or surgery which, in the judgement of the investigator, puts the subject "at risk" or is likely to modify his handling of the study drug;
- suffering from any acute or chronic systemic disease or disorder;
- history of hypersensitivity or intolerance to fibrate drugs;
- regular use of sedatives, hypnotics, tranquilizers or any other addictive substances;
- signs, symptoms and laboratory test values outside the clinically acceptable "normal range" for healthy subjects;
- history or evidence of acute or chronic alcohol abuse (>14 drinks per week);
- excessive consumption (> 5 cups/day) of tea, coffee, chocolate, and/or other xanthine-containing food or beverages;
- positive HIV or HCV test, and/or a positive HBsAg test;
- received blood or plasma derivatives in the year preceding the initiation of the study;
- plasma donation in the 7 days preceding the initiation of the study and blood donation in the 56 days preceding the initiation of the study or intention to make blood or plasma donation during the study or within the three months following the study completion;
- be pregnant or lactating (All females of child-bearing potential must have a negative pregnancy test at screening. Over the course of the study, females must practice a method of contraception with greater than 90% reliability, or be sterile or postmenopausal);
- drug treatment during the two weeks preceding the study, except for women who may continue taking appropriate birth control medication;
- drug treatment that could lead to induction of hepatic microsomal enzymes (e.g., carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin) within 3 months of the study start;
- subject who has participated in another clinical study of any kind (drug or device) in the month immediately prior to the start of this study;
- subject who, in the judgement of the investigator, is likely to be non-compliant or uncooperative during the study;

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<p>Exclusion Criteria (continued):</p> <ul style="list-style-type: none">• subject who has forfeited his freedom by administrative or legal award or who is under guardianship;• subject who cannot be contacted in case of emergency.
<p>Test Products (name, dose, lot/batch number, expiry/reassay date, potency, administration):</p> <p>IDD-PTM fenofibrate, RTP Pharma Inc., Canada; lot number: 003; reassay date: 2000/10; potency: /tablet; administered as a 1 x 160 mg tablet.</p>
<p>Duration of Treatment:</p> <p>Subjects were given IDD-PTM (fenofibrate) under fasting (A), standard (low-fat) fed (B), and high-fat fed (C) conditions. Subjects were confined to the clinical facility from at least 22:00 on the night prior to drug administration, until after the 24.0-hour post-dose blood draw, in each period. Clinical procedures (return visits to the clinical facility) extended until approximately 120 hours post-dose.</p>
<p>Criteria for Evaluation:</p> <p>Pharmacokinetics/Bioavailability:</p> <p>The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, % extrapolated, t_{max}, K_{el}, $t_{1/2}$, and F_{rel}.</p> <p>Primary parameters: AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.</p> <p>Secondary parameters: % extrapolated, t_{max}, K_{el}, $t_{1/2}$ and F_{rel}.</p> <p>Safety:</p> <p>Vital signs (pulse rate, blood pressure, respiratory rate, and oral temperature) were performed for each subject (seated for at least 3 minutes) during the evening prior to drug administration in Periods 1, 2, and 3.</p> <p>An alcohol breath test, a urine drug screen, and a urine pregnancy test (for female subjects of child-bearing potential) were performed for each subject during the evening prior to drug administration in Periods 1, 2, and 3.</p> <p>Throughout the study, subjects were monitored for adverse events. At the times of admission, subjects were asked a standard probe question concerning the onset of a new illness since the last visit, and at the time of discharge, each subject was asked how he/she was feeling.</p> <p>Laboratory tests (hematology, biochemistry, and urinalysis), physical examinations, and vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature) were performed between 4 and 9 days after the last blood draw of the last period, or after subject withdrawal.</p>
<p>Statistical Methods:</p> <p>Descriptive statistics with means, standard deviations, coefficients of variations and range (min.) and (max.). ANOVA incorporating the gender effect for ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} and untransformed t_{max}, K_{el} and $t_{1/2}$ at the alpha level of 0.05. Ratio of geometric least-squares means (A/B), (C/B) and (C/A) and 90% geometric confidence interval around the ratio for ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.</p>

Pharmacokinetics/Bioavailability Results:

Through the study there were no significant protocol deviations to confound the pharmacokinetics and bioavailability analyses. Study results were not corrected for drug potency.

- Ratios (A/B) of least-squares means for AUC_{0-1} , $AUC_{0-\infty}$, and C_{max} were 89.71%, 90.04% and 61.81%, respectively, demonstrating a slightly lower extent of absorption and a lower rate of absorption of IDD-PTM fenofibrate tablet 160 mg administered under fasting conditions (A) compared to IDD-PTM fenofibrate tablet 160 mg administered immediately following a low-fat meal (B).
- Ratios (C/B) of least-squares means for AUC_{0-1} , $AUC_{0-\infty}$, and C_{max} were 106.91%, 106.93% and 99.84%, respectively, demonstrating a slightly higher extent of absorption and a slightly lower rate of absorption of IDD-PTM fenofibrate tablet 160 mg administered immediately after a high-fat meal (C) compared to IDD-PTM fenofibrate tablet 160 mg administered immediately following a low-fat meal (B).
- Ratios (C/A) of least-squares means for AUC_{0-1} , $AUC_{0-\infty}$, and C_{max} were 119.18%, 118.76% and 161.51%, respectively, demonstrating a slightly higher extent of absorption and a higher rate of absorption of IDD-PTM fenofibrate tablet 160 mg administered immediately after a high-fat meal (C) compared to IDD-PTM fenofibrate tablet 160 mg administered under fasting conditions (A).
- ANOVA detected a statistically significant difference between treatments for ln-transformed AUC_{0-1} , $AUC_{0-\infty}$, C_{max} and untransformed $t_{1/2}$ and K_{el} .
- ANOVA also detected a statistically significant gender by treatment interaction for ln-transformed AUC_{0-1} and $AUC_{0-\infty}$.
- ANOVA did not detect any statistically significant difference between treatments for untransformed t_{max} .

Safety Results:

The Principal Investigator judged the reported deviations unlikely to have affected the results of the study.

Physical examinations, vital signs, ECGs, and laboratory tests were performed at the times specified in the protocol. Clinically significant abnormal post-study laboratory results were obtained for three subjects (glucose, creatine kinase, and white blood cells in urine). Upon being repeated, these tests yielded normal or not clinically significant results. All other final post-study laboratory test results and vital signs measurements were within normal limits or judged to be not clinically significant by a Medical Sub-Investigator.

Alcohol breath tests, urine drug screens, and urine pregnancy tests (for female subjects of child-bearing potential) were performed for each subject at the times specified in the protocol. All tests yielded negative results for subjects completing the study.

Of the 39 post-dose adverse events reported, 14 adverse events were judged unrelated to the study medication, 9 were judged unlikely related, 16 were judged possibly related, and 0 were judged probably related. The severity at onset was mild for 34 adverse events, 1 was assessed as moderate, and 1 was assessed as severe. The severity of the remaining adverse events was not graded as these events are associated with clinically significant abnormal laboratory results. No serious adverse events were reported.

Safety Results (continued):

The reported AEs post-dose are summarized as follows:

Deaths: None
Discontinuations from AEs: One subject (syncope and nausea)
Serious or severe AEs: Syncope (1) (unrelated to study drug)
Probably drug-related AEs: None
Possibly drug-related AEs: Asthenia (1), creatine PK ↑ (1), dizziness (1), dyspepsia (1), headache (4), myalgia (3), nausea (2), oesophagitis (1), back pain (2)
Unlikely drug-related AEs: Chills (1), cough ↑ (1), dizziness (1), myalgia (2), pain (1), pharyngitis (2), rhinitis (1)
Unrelated AEs: edema (1), headache (3), hyperglycemia (1), injury due to accident (1), nodule subcutaneous (1), pain (4), pharyngitis (1), syncope (1), elevated white blood cells in urine (1)

Summary Conclusions:

Pharmacokinetic/Bioavailability:

Based on the 90% geometric confidence intervals of AUC_{0-4} and $AUC_{0-\infty}$ that were within the 80% - 125% range, it can be concluded that the extent of absorption of IDD-P™ fenofibrate tablet 160 mg is not influenced by food or the fat content of the test meal administered. It can also be concluded that the rate of absorption of IDD-P™ fenofibrate tablet 160 mg is not influenced by the fat content of the test meal administered but is increased when taken with food.

Safety:

All study treatments were well tolerated. One severe adverse event (syncope) was recorded and was not judged to be related to the study medication. All other adverse events were mild or moderate in intensity.

Transfer of Obligations:

No obligations were transferred. RTP Pharma retains all obligations.

Contract research organizations assisted RTP Pharma with the following:

- Clinical site activities (██████████ Address: see above)
 - Ethics committee submissions
 - Study documentation (RTP Pharma prepared the protocol)
 - Study conduct
 - Clinical study report
- Analytical site activities (██████████ Address: see above)
 - Analytical assays
 - Statistical analyses
 - Analytical report

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Project No. FEN100-C05 / 00184

Comparative Bioavailability of IDD-P™ Fenofibrate Tablet 160 mg Under Fasting, Low-fat Fed and High-fat Fed Conditions in Healthy Subjects

Financial Disclosure:

As per forms FDA 3455 and FDA 3454, there were no disclosable financial arrangements or interests between the study sponsor (RTP Pharma Inc.) and clinical study site personnel of [REDACTED] whereby the value of compensation to [REDACTED] could be influenced by the outcome of the study.

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Table 1 FEN100-C05. Summary of Pharmacokinetic Parameters for IDD-PTM Fenofibrate 160 mg Tablet lot #003 Administered Under Fasting (A), Low-fat Fed (B) and High-fat Fed (C) Conditions

Parameters	IDD-PTM fenofibrate tablet 160 mg formulation								
	Fasting (A)			Low-fat fed (B)			High-fat fed (C)		
	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC ₀₋₄ (ng·h/mL)	132301.14	31194.10	23.58	147713.23	35769.60	24.22	156731.95	36382.76	23.21
AUC _{0-∞} (ng·h/mL)	135032.51	32025.51	23.72	150139.43	36238.46	24.14	159318.08	36663.31	23.01
C _{max} (ng/mL)	735151	1943.44	26.44	11649.40	2171.75	18.64	11760.62	2893.11	24.60
% extrapolated (%)	1.99	1.24	62.28	1.63	0.93	57.18	1.66	0.71	42.75
t _{max} (h)	2.82	1.14	40.52	2.86	1.13	39.30	3.09	1.54	49.83
K _a (h ⁻¹)	0.0367	0.0078	21.20	0.0420	0.0104	24.88	0.0423	0.0113	26.78
t _{1/2} (h)	19.79	4.74	23.96	17.71	5.21	29.43	17.52	4.63	26.42
F _{rel} (vs low fat) (%)	90.94	12.86	14.14	100.0	0.00	-	107.37	14.14	13.17
F _{rel} (vs fasting) (%)	100.0	0.00	-	112.22	16.92	15.08	119.89	20.58	17.16

Table 2 FEN100-C05. Summary of Treatment Comparisons for IDD-PTM Fenofibrate 160 mg Tablet lot #003 When Administered Under Fasting Conditions (A) Versus Low-fat Fed Conditions (B), Under High-fat Fed Conditions (C) Versus Low-fat Fed Conditions (B) and Under High-fat Fed Conditions (C) Versus Fasting Conditions (A)

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of LS Means ¹	Ratio of Arithmetic Means ²	90% Confidence Interval ³		Intra-Subject CV
				Lower	Upper	
				Upper		
AUC ₀₋₄	IDD-PTM fenofibrate, fasting (A) vs IDD-PTM fenofibrate, low-fat meal (B)	89.71%	89.57%	85.58%	94.04%	9.29%
	IDD-PTM fenofibrate, high-fat meal (C) vs IDD-PTM fenofibrate, low-fat meal (B)	106.91%	106.11%	101.97%	112.09%	
	IDD-PTM fenofibrate, high-fat meal (C) vs IDD-PTM fenofibrate, fasting (A)	119.18%	118.47%	113.68%	124.95%	
AUC _{0-∞}	IDD-PTM fenofibrate, fasting (A) vs IDD-PTM fenofibrate, low-fat meal (B)	90.04%	89.94%	85.97%	94.29%	9.10%
	IDD-PTM fenofibrate, high-fat meal (C) vs IDD-PTM fenofibrate, low-fat meal (B)	106.93%	106.11%	102.09%	112.00%	
	IDD-PTM fenofibrate, high-fat meal (C) vs IDD-PTM fenofibrate, fasting (A)	118.76%	117.98%	113.38%	124.40%	
C _{max}	IDD-PTM fenofibrate, fasting (A) vs IDD-PTM fenofibrate, low-fat meal (B)	61.81%	63.11%	55.95%	68.30%	19.81%
	IDD-PTM fenofibrate, high-fat meal (C) vs IDD-PTM fenofibrate, low-fat meal (B)	99.84%	100.95%	90.33%	110.35%	
	IDD-PTM fenofibrate, high-fat meal (C) vs IDD-PTM fenofibrate, fasting (A)	161.51%	159.98%	146.13%	178.51%	

¹ Calculated using least-squares means (ln-transformed data).

² Calculated using arithmetic means (untransformed data).

³ 90% Geometric confidence interval based on ln-transformed data

Figure 1 Fenofibric Acid Mean Concentration - (Time profile; n = 22)

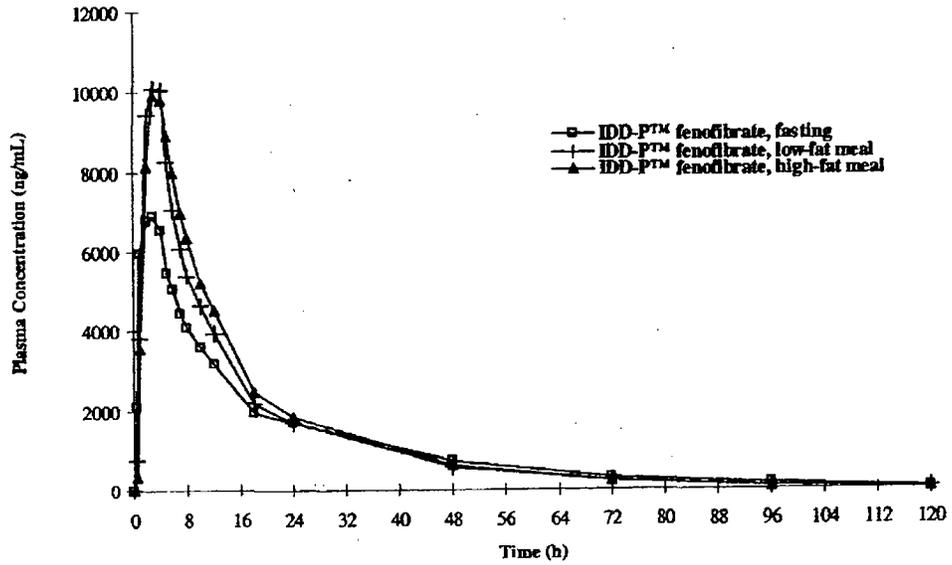
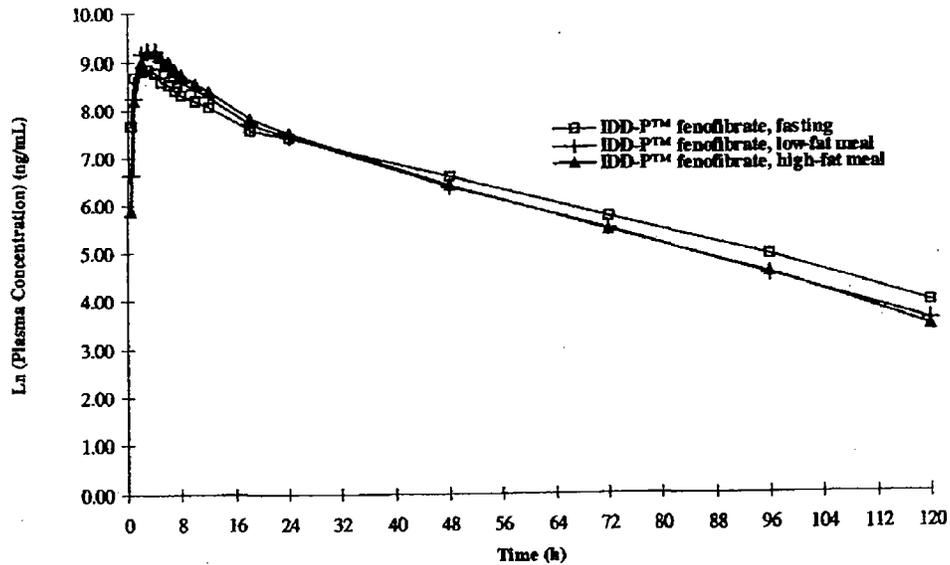


Figure 2 Fenofibric Acid Ln (Mean Concentration)- (Time profile; n = 22)



1. Title page

Title: Comparative bioavailability of IDD-PTM fenofibrate tablet 160 mg with micronized fenofibrate capsule 200 mg in healthy fed subjects

Test drug: IDD-PTM fenofibrate 160 mg tablet and Tricor™, micronized fenofibrate, 200 mg capsule

Indication: This was a single center, open-label, randomized, 2-way crossover study to assess the bioavailability of IDD-PTM fenofibrate tablet 160 mg relative to that of Tricor™, fenofibrate (micronized) capsule 200 mg under standard low-fat meal conditions. Doses were separated by a washout period of 10 days.

Sponsor's name and address: RTP Pharma Inc., 1000 chemin du Golf, Verdun, Quebec, Canada, H3E 1H4
Contact: Dr. Pol-Henri Guivarc'h; tel. (514) 362-9818 ext. 264;

Study number(s): _____

Development phase: Phase I pharmacokinetic study

Study dosing dates: November 13, 2000 – November 23, 2000
Study Completion Date: January 11, 2001

Investigator(s): _____

Investigator _____

Date: May 18, 2001

Confidentiality statement: This document is strictly confidential. It was developed for RTP Pharma Inc. and should not be disclosed to a third party, with the exception of regulatory agencies and study audit personnel. Reproduction, modification, or adaptation, in part or in total, is strictly forbidden without prior written approval by RTP Pharma Inc.

Project No. FEN100-C06 / 00185
 Comparative Bioavailability of IDD-PTM Fenofibrate Tablet 160 mg with Micronized Fenofibrate Capsule 200 mg
 in Healthy Fed Subjects

2. Study Synopsis

Name of Sponsor/Company: RTP Pharma Inc., Canada	
Name of Finished Product: IDD-PTM fenofibrate	
Name of Active Ingredient: Fenofibrate	
Title of Study: Comparative bioavailability of IDD-PTM fenofibrate tablet 160 mg with micronized fenofibrate capsule 200 mg in healthy fed subjects	
Investigator(s): Investigator: _____ Sub-Investig: _____	
Study Centre(s): Clinical: _____ Analytical: _____	
Publication (reference): None at the date of this report	
Study Period (IRB approval to last scheduled visit): October 25, 2000, to December 7, 2000	Phase of Development: Phase I study
Scheduled dosing days: Period 1: November 13, 2000 Period 2: November 23, 2000	Type of Study: Single dose pharmacokinetics- Comparative bioavailability
Objectives: The objective of this study was to assess the bioavailability of IDD-PTM fenofibrate 160 mg tablet relative to that of Tricor™, fenofibrate (micronized) 200 mg capsule under standard low-fat meal conditions.	

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Methodology:

This was a single-center, open-label, randomized, two-treatment, two-period, two-sequence crossover study to assess the bioavailability of IDD-PTM fenofibrate tablet 160 mg relative to that of Tricor™, fenofibrate (micronized) capsule 200 mg under standard low-fat meal conditions. Doses were separated by a washout period of 10 days. Twenty-eight (28) healthy, adult, non-smokers (for at least 3 months) were enrolled in this study. Subjects were confined from at least 22:00 on the night before dosing until after the 24.0-hour post-dose blood draw in each period.

After a supervised overnight fast of at least 9.5 hours and subsequent consumption of the low-fat test meal, subjects were administered IDD-PTM fenofibrate 160 mg tablet (A), or Tricor™, fenofibrate (micronized formulation) 200 mg capsule (B), as one tablet or capsule. The test meal was consumed over an interval of 15 minutes and was completed within 5 minutes prior to drug administration.

All blood samples were drawn into blood collection tubes (1 x 7 mL) containing EDTA prior to drug administration and 0.500, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 18.0, 24.0, 48.0, 72.0, 96.0, and 120.0 hours post-dose, in each period. All blood samples were collected via direct venipuncture.

Blood samples were [redacted] for 10 minutes at approximately 4°C. Two aliquots of at least 1.2 mL of plasma (when possible) were dispensed into [redacted] tubes as soon as possible, before being transferred to a -20°C±5°C freezer, pending analysis.

Number of Subjects (planned and analyzed):

Of the 28 healthy, adult, non-smokers (8 males [M] and 20 females [F]) who were dosed, 2 did not complete the study. Subject No. 01 (F) elected to withdraw from the study prior to Period 2 dosing, due to a personal reason. Subject No. 08 (F) elected to withdraw from the study prior to Period 2 dosing, because of concomitant medications she had taken. Thus, 26 subjects (8 males and 18 females) completed the study. The data of the first 24 subjects who completed the study were used for the pharmacokinetic analysis. Safety analysis and procedures were performed for the 28 subjects who were dosed.

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Inclusion and Exclusion Criteria:

Inclusion Criteria:

- 18 to 55 years old;
- weight within $\pm 20\%$ of the ideal body weight of the Metropolitan Insurance Company scale;
- deemed "normal" following a comprehensive clinical assessment (detailed medical history, complete physical examination, and ECG) and laboratory investigations (hematology, blood chemistry, urinalysis), the results of which must be within the normal range and/or clinically acceptable for healthy subjects;
- non-smoker, non-tobacco user for at least 3 months;
- negative drug urine screen and alcohol urine or breath test;
- subjects with "normal" dietary habits (i.e., no restrictive regimen) and willing to eat the study test meal;
- informed subjects accepting the study constraints and restrictions and having signed the informed consent.

Exclusion Criteria:

- history of major medical/psychiatric illness or surgery which, in the judgement of the investigator, puts the subject "at risk" or is likely to modify his handling of the study drug;
- suffering from any acute or chronic systemic disease or disorder;
- history of hypersensitivity or intolerance to fibrate drugs;
- regular use of sedatives, hypnotics, tranquilizers or any other addictive substances;
- signs, symptoms, and laboratory test values outside the clinically acceptable "normal range" for healthy subjects;
- history or evidence of acute or chronic alcohol abuse (>14 drinks per week);
- excessive consumption (> 5 cups/day) of tea, coffee, chocolate, and/or other xanthine-containing food or beverages;
- positive HIV or HCV test, and/or a positive HBsAg test;
- received blood or plasma derivatives in the year preceding the initiation of the study;
- plasma donation in the 7 days preceding the initiation of the study and blood donation in the 56 days preceding the initiation of the study or intention to make blood or plasma donation during the study or within the three months following the study completion;
- be pregnant or lactating (All females of child-bearing potential must have a negative pregnancy test at screening. Over the course of the study, females must practice a method of contraception with greater than 90% reliability, or be sterile or postmenopausal);
- drug treatment during the two weeks preceding the study, except for women who may continue taking appropriate birth control medication;
- drug treatment that could lead to induction of hepatic microsomal enzymes (e.g., carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin) within 3 months of the study start;
- subject who has participated in another clinical study of any kind (drug or device) in the month immediately prior to the start of this study;
- subject who, in the judgement of the investigator, is likely to be non-compliant or uncooperative during the study;
- subject who has forfeited his freedom by administrative or legal award or who is under guardianship;
- subject who cannot be contacted in case of emergency.

Test Products (name, dose, lot/batch number, expiry/reassay date, potency, administration):

IDD-PTM fenofibrate, RTP Pharma Inc., Canada; batch number: 003; reassay date: 12/2000; potency: ██████████; administered as a 1 x 160 mg tablet.

Tricor™, fenofibrate (micronized formulation), Laboratoires Fournier S.A., France; lot number: 605402E21; expiry date: 01/2002; potency: ██████████ administered as a 1 x 200 mg capsule.

Duration of Treatment:

Subjects were given IDD-PTM fenofibrate or Tricor™, fenofibrate (micronized formulation), under standard low-fat meal conditions. Subjects were confined to the clinical facility from at least 22:00 on the night prior to drug administration, until after the 24.0-hour post-dose blood draw, in each period. Clinical procedures (return visits to the clinical facility) extended until approximately 120 hours post-dose.

Criteria for Evaluation:

Pharmacokinetics/Bioavailability:

The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-4} , AUC_{0-24} , C_{max} , % extrapolated, t_{max} , K_{el} , $t_{1/2}$, and F_{rel} .

Primary parameters: AUC_{0-4} , AUC_{0-24} and C_{max} .

Secondary parameters: % extrapolated, t_{max} , K_{el} , $t_{1/2}$ and F_{rel} .

Safety:

Vital signs (respiratory rate and oral temperature; blood pressure and pulse rate, after having been seated for at least 3 minutes) were performed for each subject during the evening prior to drug administration in Periods 1 and 2.

An alcohol breath test, a urine drug screen, and a urine pregnancy test (for female subjects of child-bearing potential) were performed for each subject during the evening prior to drug administration in Periods 1 and 2.

Throughout the study, subjects were monitored for adverse events. At the times of admission, subjects were asked a standard probe question concerning the onset of a new illness since the last visit, and at the time of discharge, each subject was asked how he/she was feeling.

Laboratory tests (hematology, biochemistry, and urinalysis), physical examinations, vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature), and urine pregnancy test (females of child-bearing potential) were performed between 4 and 9 days after collection of the last blood draw of the last period, or after subject withdrawal.

Statistical Methods:

Descriptive statistics with means, standard deviations, coefficients of variations and range (min.) and (max.). ANOVA incorporating the gender effect for ln-transformed AUC_{0-4} , AUC_{0-24} and C_{max} and untransformed t_{max} , K_{el} and $t_{1/2}$ at the alpha level of 0.05. Ratio of geometric least-squares means (A/B) and 90% geometric confidence interval around the ratio for ln-transformed AUC_{0-4} , AUC_{0-24} and C_{max} .

Inclusion and Exclusion Criteria:

Inclusion Criteria:

- 18 to 55 years old;
- weight within $\pm 20\%$ of the ideal body weight of the Metropolitan Insurance Company scale;
- deemed "normal" following a comprehensive clinical assessment (detailed medical history, complete physical examination, and ECG) and laboratory investigations (hematology, blood chemistry, urinalysis), the results of which must be within the normal range and/or clinically acceptable for healthy subjects;
- non-smoker, non-tobacco user for at least 3 months;
- negative drug urine screen and alcohol urine or breath test;
- subjects with "normal" dietary habits (i.e., no restrictive regimen) and willing to eat the study test meal;
- informed subjects accepting the study constraints and restrictions and having signed the informed consent.

Exclusion Criteria:

- history of major medical/psychiatric illness or surgery which, in the judgement of the investigator, puts the subject "at risk" or is likely to modify his handling of the study drug;
- suffering from any acute or chronic systemic disease or disorder;
- history of hypersensitivity or intolerance to fibrate drugs;
- regular use of sedatives, hypnotics, tranquilizers or any other addictive substances;
- signs, symptoms, and laboratory test values outside the clinically acceptable "normal range" for healthy subjects;
- history or evidence of acute or chronic alcohol abuse (>14 drinks per week);
- excessive consumption (> 5 cups/day) of tea, coffee, chocolate, and/or other xanthine-containing food or beverages;
- positive HIV or HCV test, and/or a positive HBsAg test;
- received blood or plasma derivatives in the year preceding the initiation of the study;
- plasma donation in the 7 days preceding the initiation of the study and blood donation in the 56 days preceding the initiation of the study or intention to make blood or plasma donation during the study or within the three months following the study completion;
- be pregnant or lactating (All females of child-bearing potential must have a negative pregnancy test at screening. Over the course of the study, females must practice a method of contraception with greater than 90% reliability, or be sterile or postmenopausal);
- drug treatment during the two weeks preceding the study, except for women who may continue taking appropriate birth control medication;
- drug treatment that could lead to induction of hepatic microsomal enzymes (e.g., carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin) within 3 months of the study start;
- subject who has participated in another clinical study of any kind (drug or device) in the month immediately prior to the start of this study;
- subject who, in the judgement of the investigator, is likely to be non-compliant or uncooperative during the study;
- subject who has forfeited his freedom by administrative or legal award or who is under guardianship;
- subject who cannot be contacted in case of emergency.

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Test Products (name, dose, lot/batch number, expiry/reassay date, potency, administration):

IDD-P™ fenofibrate, RTP Pharma Inc., Canada; batch number: 003; reassay date: 12/2000; potency: █████ administered as a 1 x 160 mg tablet.

Tricor™, fenofibrate (micronized formulation), Laboratoires Fournier S.A., France; lot number: 605402E21; expiry date: 01/2002; potency: █████ administered as a 1 x 200 mg capsule.

Duration of Treatment:

Subjects were given IDD-P™ fenofibrate or Tricor™, fenofibrate (micronized formulation), under standard low-fat meal conditions. Subjects were confined to the clinical facility from at least 22:00 on the night prior to drug administration, until after the 24.0-hour post-dose blood draw, in each period. Clinical procedures (return visits to the clinical facility) extended until approximately 120 hours post-dose.

Criteria for Evaluation:

Pharmacokinetics/Bioavailability:

The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , % extrapolated, t_{max} , K_{el} , $t_{1/2}$, and F_{rel} .

Primary parameters: AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Secondary parameters: % extrapolated, t_{max} , K_{el} , $t_{1/2}$ and F_{rel} .

Safety:

Vital signs (respiratory rate and oral temperature; blood pressure and pulse rate, after having been seated for at least 3 minutes) were performed for each subject during the evening prior to drug administration in Periods 1 and 2.

An alcohol breath test, a urine drug screen, and a urine pregnancy test (for female subjects of child-bearing potential) were performed for each subject during the evening prior to drug administration in Periods 1 and 2.

Throughout the study, subjects were monitored for adverse events. At the times of admission, subjects were asked a standard probe question concerning the onset of a new illness since the last visit, and at the time of discharge, each subject was asked how he/she was feeling.

Laboratory tests (hematology, biochemistry, and urinalysis), physical examinations, vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature), and urine pregnancy test (females of child-bearing potential) were performed between 4 and 9 days after collection of the last blood draw of the last period, or after subject withdrawal.

Statistical Methods:

Descriptive statistics with means, standard deviations, coefficients of variations and range (min.) and (max.). ANOVA incorporating the gender effect for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} and untransformed t_{max} , K_{el} and $t_{1/2}$ at the alpha level of 0.05. Ratio of geometric least-squares means (A/B) and 90% geometric confidence interval around the ratio for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Pharmacokinetics/Bioavailability Results:

Through the study there were no significant protocol deviations to confound the pharmacokinetics and bioavailability analyses. Study results were not corrected for drug potency.

- Ratios (A/B) of least-squares means for AUC_{0-4} , $AUC_{0-\infty}$, and C_{max} were 94.09%, 93.69% and 110.73%, respectively, demonstrating a slightly lower extent of absorption and a slightly higher rate of absorption of IDD-P™ fenofibrate tablet 160 mg administered under low-fat fed conditions (A) compared to Tricor™, fenofibrate (micronized) capsule 200 mg administered immediately following a low-fat meal (B).
- ANOVA detected a statistically significant difference between treatments for ln-transformed $AUC_{0-\infty}$, C_{max} and untransformed t_{max} and $t_{1/2}$.
- ANOVA also detected a statistically significant difference between genders for ln-transformed C_{max} and a statistically significant treatment by gender interaction for untransformed t_{max} .
- ANOVA did not detect any statistically significant difference between treatments for ln-transformed AUC_{0-4} and untransformed K_{el} .

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Safety Results:

The Principal Investigator judged the reported protocol deviations unlikely to have affected the results or the conclusions of the study.

Physical examinations, vital signs, ECGs, and laboratory tests were performed at the times specified in the protocol. One subject who presented with a low white blood cell (WBC) count at the time of screening, had a further decline of 23% in white blood cells at the time of the post-study procedures. The post-study procedures result was judged to be clinically significant, but, upon repeat testing, the white blood cell count had returned to approximately the baseline value, and was judged to be not clinically significant. All other post-study laboratory test results and vital signs measurements were within normal limits or judged to be not clinically significant by a Medical Sub-Investigator.

Alcohol breath tests, urine drug screens, and urine pregnancy tests were performed for each subject at the times specified in the protocol. All tests yielded negative results for subjects completing the study.

Of the 33 post-dose adverse events reported, 2 adverse events were judged to be probably related to the study medication, 13 were judged possibly related, 9 were judged unlikely related, and 9 were judged unrelated. Twenty-seven (27) adverse events were mild in intensity, 5 were moderate, and 1 was not graded in intensity, as this adverse event was associated with a clinically significant post-study laboratory result (low white blood cell count). No serious or severe adverse events were reported.

The reported post-dose adverse events are summarized as follows:

Deaths:	None
Discontinuations from AEs:	None
Serious or severe AEs:	None
Probably drug-related AEs:	Headache (2)
Possibly drug-related AEs:	Abdominal pain (2), headache (6), pruritis (2), flatulence (2), diarrhea (1)
Unlikely drug-related AEs:	Pharyngitis (2), menorrhagia (1), asthenia (1), polyuria (2), vasodilation (1), flatulence (1), leukopenia (1)
Unrelated AEs:	Pain (3), edema (1), conjunctivitis (2), abdominal pain (1), ecchymosis (1), vaginitis (1).

Summary Conclusions:

Pharmacokinetic/Bioavailability:

Based on the 90% geometric confidence intervals of $AUC_{0-\infty}$, AUC_{0-12} , and C_{max} that were within the 80% - 125% range, it can be concluded that the rate and extent of absorption of IDD-PTM fenofibrate tablet 160 mg and Tricor™, fenofibrate (micronized) 200 mg capsule are comparable when administered immediately following a low-fat meal.

Safety:

All adverse events were mild or moderate in intensity thus, the study treatments were well tolerated.

Transfer of Obligations:

No obligations were transferred. RTP Pharma retains all obligations.

Contract research organizations assisted RTP Pharma with the following:

- Clinical site activities ([redacted] Address: see above)
 - Ethics committee submissions
 - Study documentation (RTP Pharma prepared the protocol)
 - Study conduct
 - Clinical study report
- Analytical site activities ([redacted] Address: see above)
 - Analytical assays
 - Statistical analyses
 - Analytical report

Financial Disclosure:

As per forms FDA 3455 and FDA 3454, there were no disclosable financial arrangements or interests between the study sponsor (RTP Pharma Inc.) and clinical study site personnel of [redacted] whereby the value of compensation to [redacted] could be influenced by the outcome of the study.

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Project No. FEN100-C06 / 00185
 Comparative Bioavailability of IDD-PTM Fenofibrate Tablet 160 mg with Micronized Fenofibrate Capsule 200 mg
 in Healthy Fed Subjects

Table 1. FEN100-C06. Summary of Pharmacokinetic Parameters for IDD-PTM Fenofibrate 160 mg Tablet lot #003 (A) and Tricor™ Micronized Fenofibrate 200 mg Capsule (B) Given under Low-fat Fed Conditions

Parameters	IDD-PTM fenofibrate, low-fat meal (A)			Micronized fenofibrate, low-fat meal (B)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC ₀₋₄ (ng·h/mL)	137587.71	48203.28	35.03	149272.07	58621.21	39.27
AUC _{0-∞} (ng·h/mL)	140067.57	49380.22	35.25	152599.13	60529.39	39.67
C _{max} (ng/mL)	11204.05	2507.73	22.38	10401.84	3039.54	29.22
% extrapolated (%)	1.76	1.13	63.91	2.12	1.22	57.83
t _{max} (h)	3.21	1.10	34.36	4.75	0.90	18.88
K _{el} (h ⁻¹)	0.0507	0.0220	43.51	0.0449	0.0177	39.37
t _{1/2} (h)	15.72	5.47	34.76	17.77	6.51	36.63
F _{rel} (vs low fat) (%)	94.05	12.36	13.14	100.00	0.00	-

Table 2. FEN100-C06. Summary of Treatment Comparisons for IDD-PTM Fenofibrate 160 mg Tablet lot #003 (A) versus Tricor™ Micronized Fenofibrate 200 mg Capsule (B) Given under Low-fat Fed Conditions

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of LS Means ¹	Ratio of Arithmetic Means ²	90% Confidence Interval ³		Intra-Subject CV
				Lower	Upper	
AUC ₀₋₄	IDD-PTM fenofibrate, low-fat meal (A) vs Micronized fenofibrate, low-fat meal (B)	94.09%	92.17%	89.15%	99.31%	10.27%
AUC _{0-∞}	IDD-PTM fenofibrate, low-fat meal (A) vs Micronized fenofibrate, low-fat meal (B)	93.69%	91.79%	89.09%	98.53%	9.58%
C _{max}	IDD-PTM fenofibrate, low-fat meal (A) vs Micronized fenofibrate, low-fat meal (B)	110.73%	107.71%	101.84%	120.39%	15.98%

¹ Calculated using least-squares means (ln-transformed data).

² Calculated using arithmetic means (untransformed data).

³ 90% Geometric confidence interval based on ln-transformed data

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Figure 1. Fenofibric Acid Mean Concentration - (Time profile; n = 24)

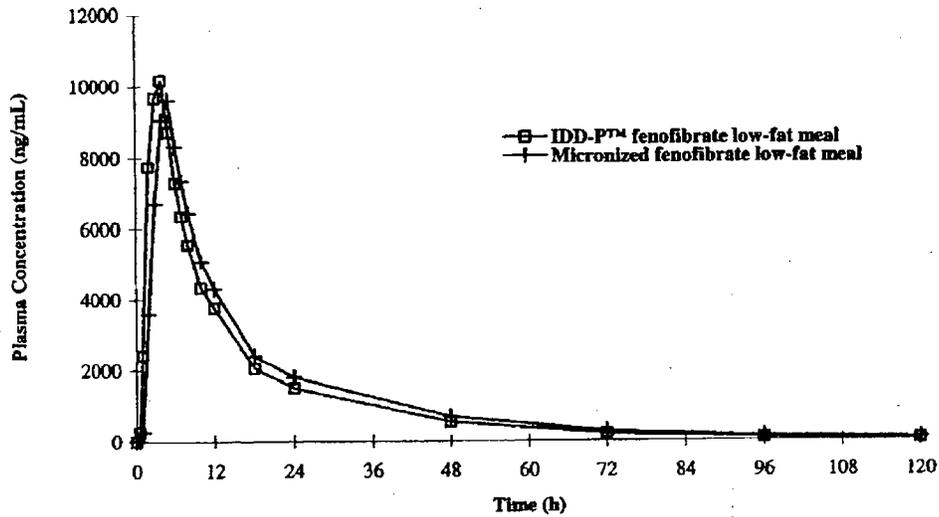
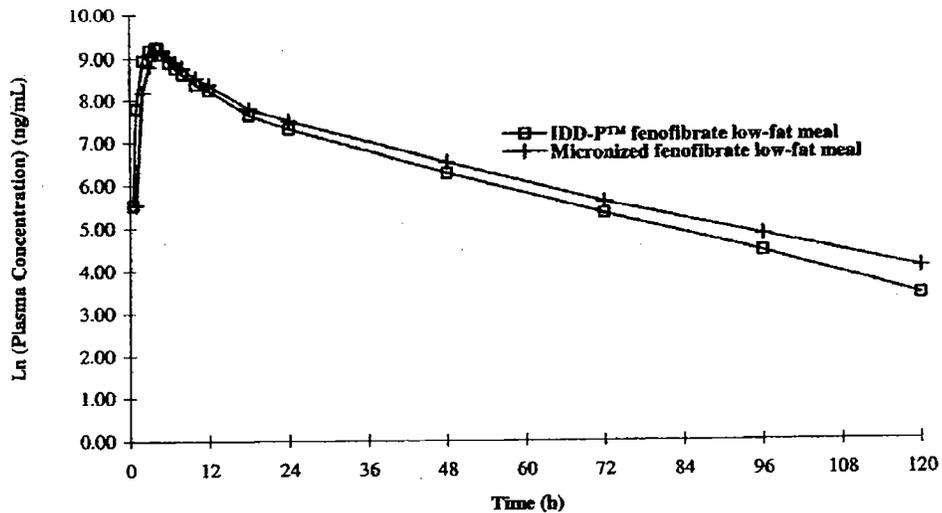


Figure 2. Fenofibric Acid Ln (Mean Concentration)- (Time profile; n = 24)



1. Title page

Title: Comparative bioavailability of IDD-P™ fenofibrate tablet 160 mg with micronized fenofibrate capsule 200 mg in healthy fasting subjects

Test drug: IDD-P™ fenofibrate tablet 160 mg and Tricor™ micronized fenofibrate 200 mg capsule

Indication: This was a single center, open-label, randomized, 2-way crossover study to assess the bioavailability of IDD-P™ fenofibrate tablet 160 mg relative to that of Tricor™ micronized fenofibrate capsule 200 mg under standard fasting conditions. Doses were separated by a washout period of 10 days.

Sponsor's name and address: RTP Pharma Inc., 1000 chemin du Golf, Verdun, Quebec, Canada, H3E 1H4

Study number(s): _____

Development phase: Phase I pharmacokinetic study

Study dosing dates: October 6, 2001 – October 16, 2001
Study Completion Date: November 22, 2001

Investigator(s): _____

Investigator _____

Date: December 18, 2001

Confidentiality statement: This document is strictly confidential. It was developed for RTP Pharma Inc. and should not be disclosed to a third party, with the exception of regulatory agencies and study audit personnel. Reproduction, modification, or adaptation, in part or in total, is strictly forbidden without prior written approval by RTP Pharma Inc.

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Project No. FEN100-C07 / 00267
 Comparative Bioavailability of IDD-PTM Fenofibrate Tablet 160 mg with Micronized Fenofibrate Capsule
 200 mg in Healthy Fasting Subjects

2. Study Synopsis

Name of Sponsor/Company: RTP Pharma Inc., Canada	
Name of finished Product: IDD-PTM Fenofibrate	
Name of Active Ingredient: Fenofibrate	
Title of Study: Comparative bioavailability of IDD-PTM fenofibrate tablet 160 mg with micronized fenofibrate capsule 200 mg in healthy fasting subjects.	
Investigator(s): Investigator: a [REDACTED] Sub-Investigator (s): [REDACTED]	
Study Centre(s): [REDACTED]	
Publication (reference): None at the date of this report	
Study Period (IRB approval to last scheduled visit): November 1, 2000, to November 22, 2001	Phase of Development: Phase I study
Scheduled dosing days: Period 1: October 6, 2001 Period 2: October 16, 2001	Type of Study: Single dose pharmacokinetic- Comparative bioavailability
Objectives: To assess the bioavailability of IDD-PTM fenofibrate tablet 160 mg relative to that of Tricor™ micronized fenofibrate capsule 200 mg under fasting conditions.	

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Methodology:

This was a single-center, open-label, single dose, randomized, two-treatment, two-period, two-sequence crossover study to assess the bioavailability of IDD-PTM fenofibrate tablet 160 mg relative to that of Tricor™, fenofibrate (micronized), capsule 200 mg under fasting conditions. Doses were separated by a washout period of 10 days. Twenty-four (24) healthy, adults (10 males and 14 females), non-smokers for at least 3 months were enrolled in this study. Subjects were confined from 21:00 on the day prior to dosing, until after the 24.0-hour post-dose blood draw in each period.

Subjects were administered 1 tablet of IDD-PTM fenofibrate 160 mg (Treatment B) or 1 capsule of Tricor™, fenofibrate (micronized) 200 mg (Treatment A) after a supervised overnight fast of at least 10 hours.

All blood samples were drawn into blood collection tubes (1 x 7 mL) containing EDTA, prior to drug administration and 0.500, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 18.0, 24.0, 48.0, 72.0, 96.0, and 120 hours post-dose, in each period. All blood draws were collected via a dead-volume catheter, when possible, and by direct venipuncture otherwise.

Blood samples were ██████████ for 10 minutes at approximately 4°C. Two aliquots of at least 1.2 mL of plasma were dispensed into ██████████ tubes as soon as possible, before being transferred to a -20°C±5°C freezer, pending analysis.

Number of Subjects (planned and analyzed):

Of the 24 healthy, adult non-smokers who were dosed, 23 completed the study. The 20 individuals (9 males and 11 females) who had completed both treatment periods and had not missed blood draws at critical time points were included in the pharmacokinetic analysis. Safety analysis and procedures were performed for the 24 subjects who were dosed.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

- 18 to 55 years old;
- weight within ±20% of the ideal body weight of the Metropolitan Insurance Company scale;
- deemed "normal" following a comprehensive clinical assessment (detailed medical history, complete physical examination, and ECG) and laboratory investigations (hematology, biochemistry, urinalysis), the results of which must be within the normal range and/or clinically acceptable for healthy subjects;
- non-smoker, non-tobacco user for at least 3 months;
- negative urine drug screen and alcohol urine or breath test;
- female subjects had to have a negative pregnancy test at screening. Over the course of the study, females had to practice a method of contraception with greater than 90% reliability, or be sterile or post-menopausal;
- subjects with "normal" dietary habits (i.e., no restrictive regimen);
- informed subjects accepting the study constraints and restrictions and having signed the informed consent.

Project No. FEN100-C07 / 00267
Comparative Bioavailability of IDD-PTM Fenofibrate Tablet 160 mg with Micronized Fenofibrate Capsule
200 mg in Healthy Fasting Subjects

Exclusion Criteria:

- history of major medical/psychiatric illness or surgery which, in the judgement of the Investigator, puts the subject "at risk" or is likely to modify his handling of the study drug;
- suffering from any acute or chronic systemic disease or disorder;
- history of hypersensitivity or intolerance to fibrate drugs;
- regular use of sedatives, hypnotics, tranquilizers or any other addictive substances;
- signs, symptoms, and laboratory test values outside the clinically acceptable "normal range" for healthy subjects;
- history or evidence of acute or chronic alcohol abuse (>14 drinks per week);
- excessive consumption (> 5 cups/day) of tea, coffee, chocolate, and/or other xanthine-containing food or beverages;
- positive HIV or HCV test, and/or a positive HBsAg test;
- received blood or plasma derivatives in the year preceding the initiation of the study;
- plasma donation in the 7 days preceding the initiation of the study and blood donation in the 56 days preceding the initiation of the study or intention to make a blood or plasma donation during the study or within the three months following the study completion;
- pregnant or lactating;
- drug treatment during the two weeks preceding the study, except for women who could continue taking appropriate birth control medication;
- drug treatment that could lead to induction of hepatic microsomal enzymes (e.g., carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin) within 3 months of the study start;
- subject who had participated in another clinical study of any kind (drug or device) in the month immediately prior to the start of this study;
- subject who, in the judgement of the Investigator, was likely to be non-compliant or uncooperative during the study;
- subject who had forfeited his freedom by administrative or legal award or who was under guardianship;
- subject who could not have been contacted in case of emergency.

Test Product (name, dose, lot/batch number, expiry/reassay date, potency, administration):

Tricor™, fenofibrate (micronized), Laboratoires Fournier, S.A., France; lot number: 694532E21; expiry date: 1NOV 2002; potency: ██████████; administered as 1 x 200 mg capsule.

IDD-PTM fenofibrate, RTP Pharma Inc., Canada; lot number: 003; reassay date: 2002/03; potency: ██████████ administered as 1 x 160 mg tablet.

Duration of Treatment:

Subjects were given either IDD-PTM fenofibrate 1 x 160 mg tablet or Tricor™, fenofibrate (micronized), capsule 200 mg under fasting conditions. Subjects were confined to the clinical facility from 21:00 on the day prior to dosing, until after the 24.0-hour post-dose blood draw, in each period. Clinical procedures (return visits to the clinical facility) extended until approximately 120 hours post-dose.

Project No. FEN100-C07 / 00267
Comparative Bioavailability of IDD-PTM Fenofibrate Tablet 160 mg with Micronized Fenofibrate Capsule
200 mg in Healthy Fasting Subjects

Criteria for Evaluation:

Pharmacokinetics/Bioavailability:

The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , % extrapolated, t_{max} , k_{el} , $t_{1/2}$, and F_{rel} .

Primary parameters: AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Secondary parameters: % extrapolated, t_{max} , k_{el} , $t_{1/2}$ and F_{rel} .

Safety:

Vital signs (respiratory rate and oral temperature; blood pressure, and pulse rate after having been seated for at least 3 minutes) were performed for each subject during the evening prior to drug administration in Periods 1 and 2.

Throughout the study, subjects were monitored for adverse events. At the times of admission, subjects were asked a standard probe question concerning the onset of a new illness since the last visit, and at the time of discharge, each subject was asked how he/she was feeling.

An alcohol breath test and a urine drug screen were performed for each subject at the time of admission for Periods 1 and 2. A urine pregnancy test was performed for all female subjects at the time of admission for Periods 1 and 2.

Laboratory tests (hematology, biochemistry, and urinalysis), urine pregnancy tests (for all female subjects), physical examinations, and vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature) were performed between 4 and 9 days after the last blood draw of the last period.

Statistical Methods:

Descriptive statistics with means, standard deviations, coefficients of variations and range (min.) and (max.). ANOVA incorporating the gender effect performed on ln-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} and untransformed t_{max} , k_{el} and $t_{1/2}$ at the alpha level of 0.05. Ratio of geometric least-squares means (B/A) and 90% geometric confidence interval around the ratio for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Pharmacokinetic/Bioavailability Results:

Through the study there were no significant protocol deviations to confound the pharmacokinetics and bioavailability analyses. Study results were not corrected for drug potency.

- Ratios (B/A) of least-squares means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 153.30%, 142.56% and 288.29%, respectively, demonstrating a higher extent and rate of absorption of the IDD-PTM fenofibrate tablet 160 mg (B) compared to Tricor™ micronized fenofibrate capsule 200 mg (A).
- ANOVA detected a statistically significant difference between treatments for ln-transformed AUC_{0-t} , $AUC_{0-\infty}$, C_{max} and untransformed t_{max} , $t_{1/2}$ and k_{el} .

Safety Results:

The Investigator judged the reported protocol deviations unlikely to have affected the results or the conclusions of the study.

Physical examinations, vital signs, ECGs, and laboratory tests were performed at the times specified in the protocol. Clinically significant abnormal post-study laboratory results were obtained for 3 subjects. Red blood cells in urine was observed in Subject Nos. 08 and 24. Repeat test for both these subjects yielded results within normal limits. Subject No. 19 had low hemoglobin (110 g/L). A repeat test still yielded a clinically significant result (113 g/L). This subject was referred to her physician for medical follow-up. All other post-study laboratory test results and vital signs measurements were within normal limits or were judged to be not clinically significant by a Medical Sub-Investigator.

Alcohol breath tests and urine drug screens were performed for each subject at the times specified in the protocol. At the time of admission for Period 2, Subject No. 16's urine drug screen test yielded a positive result for barbiturates. Pregnancy tests were performed for all female subjects at the times specified in the protocol. All tests yielded negative results for all subjects.

A total of 58 adverse events occurred during the study: 11 adverse events occurred prior to Period 1 dosing and 47 occurred post-dose of either Period 1 or 2. The relationship to the study medication of the 47 post-dose adverse events can be broken down as follows: 16 adverse events were judged "possible", 17 were judged "remote", and 14 were judged "unrelated". The pre-dose adverse event was assessed as "unrelated" to the study medication. The severity at onset was mild for 37 adverse events and was moderate for 6 adverse events. The severity of the remaining 4 adverse events was not graded, as 3 of these events were associated with clinically significant post-study laboratory results and 1 event was associated with measurable bilateral cervical lymphadenopathy. No serious, severe, or significant adverse events were reported.

The reported post-dose adverse events are summarized as follows:

Deaths:	None
Discontinuation from AEs:	None
Serious or severe AEs:	None
Probable-drug-related AEs:	None
Possible-drug-related AEs:	Chest pain (1), cough increase (1), flatulence (4), headache (4), nausea (1), pharyngitis (1), rash (1), rhinitis (3)
Remote-drug-related AEs:	Abdominal pain (1), hypochromic anemia (1), back pain (1), cough increase (1), diarrhea (1), ecchymosis (1), edema (2), flatulence (2), hematuria (2), paresthesia (2), pharyngitis (1), rhinitis (1), vasodilation (1)
Unrelated AEs:	Cough increase (1), ecchymosis (2), edema (2), headache (1), injection site pain (2), lymphadeno (1), neck pain (1), pharyngitis (1), rash (1), rhinitis (1), vasodilation (1)

Summary Conclusions:

Pharmacokinetic/Bioavailability:

Based on the least-squares means ratios (B/A) and 90% geometric confidence intervals of AUC_{0-4} , $AUC_{0-\infty}$ and C_{max} that were above the 80% - 125% range, it can be concluded that the rate and extent of absorption of IDD-P™ fenofibrate tablet 160 mg (B) are higher than the rate and extent of absorption of Tricor™ micronized fenofibrate capsule 200 mg, under fasting conditions.

Safety:

All study treatments were well tolerated.

Transfer of Obligations:

No obligations were transferred. RTP Pharma retains all obligations.

Contract research organizations assisted RTP Pharma with the following:

- Clinical site activities [REDACTED] Address: see above)
 - Ethics committee submissions
 - Study documentation (RTP Pharma prepared the protocol)
 - Study conduct
 - Clinical study report
- Analytical site activities (LA [REDACTED] Address: see above)
 - Analytical assays
 - Statistical analyses
 - Analytical report

Financial Disclosure:

As per forms FDA 3455 and FDA 3454, there were no disclosable financial arrangements or interests between the study sponsor (RTP Pharma Inc.) and clinical study site personnel or [REDACTED] whereby the value of compensation to [REDACTED] could be influenced by the outcome of the study.

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Project No. FEN100-C07 / 00267
 Comparative Bioavailability of IDD-P™ Fenofibrate Tablet 160 mg with Micronized Fenofibrate Capsule
 200 mg in Healthy Fasting Subjects

Table 1. FEN100-C07. Summary of Pharmacokinetic Parameters for Tricor™ Micronized Fenofibrate, Capsule 200 mg lot #694532E21 (A) and IDD-P™ Fenofibrate, Tablet 160 mg lot #003 (B) Given Under Standard Fasting Conditions.

Parameters	Tricor™ micronized fenofibrate (A)			IDD-P™ fenofibrate (B)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC _{0-t} (ng·h/mL)	103685.51	36922.59	35.61	154562.30	34567.83	22.36
AUC _{0-∞} (ng·h/mL)	120206.66	55916.44	46.52	161380.34	36235.15	22.45
C _{max} (ng/mL)	3078.58	1821.38	59.16	8049.29	2706.09	33.62
% extrapolated*	9.41	10.26	109.06	2.67	2.33	87.16
t _{max} (h)	6.36	6.16	96.87	3.00	1.34	44.59
k _{el} (h ⁻¹)	0.0265	0.0105	39.59	0.0356	0.0103	28.86
t _{1/2} (h)	33.00	20.44	61.93	21.05	6.17	29.29
F _{rel} (vs A) (%)	-	-	-	147.41	37.83	25.66

* For these parameters, N = 19 instead of 20.

Table 2. FEN100-C07. Summary of Treatment Comparisons for Tricor™ Micronized Fenofibrate, Capsule 200 mg lot #694532E21 (A) and IDD-P™ Fenofibrate, Tablet 160 mg lot #003 (B) Given Under Standard Fasting Conditions.

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of Arithmetic Means ¹	Ratio of LS Means ²	90% Confidence Interval ³		Intra-Subject CV
				Lower	Upper	
AUC _{0-t}	IDD-P™ fenofibrate (B) vs Tricor™ micronized fenofibrate (A)	149.07%	153.30%	141.33%	166.29%	14.79%
AUC _{0-∞} *	IDD-P™ fenofibrate (B) vs Tricor™ micronized fenofibrate (A)	134.25%	142.56%	127.29%	159.65%	20.13%
C _{max}	IDD-P™ fenofibrate (B) vs Tricor™ micronized fenofibrate (A)	261.46%	288.29%	248.48%	334.48%	27.37%

* For this parameter, N = 19 instead of 20.

¹ Calculated using arithmetic means (untransformed data).

² Calculated using least-squares means (ln-transformed data).

³ 90% Geometric confidence interval based on ln-transformed data

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Project No. FEN100-C07 / 00267
Comparative Bioavailability of IDD-P™ Fenofibrate Tablet 160 mg with Micronized Fenofibrate Capsule
200 mg in Healthy Fasting Subjects

Figure 1 Fenofibric Acid Mean Concentration - (Time profile; N = 20)

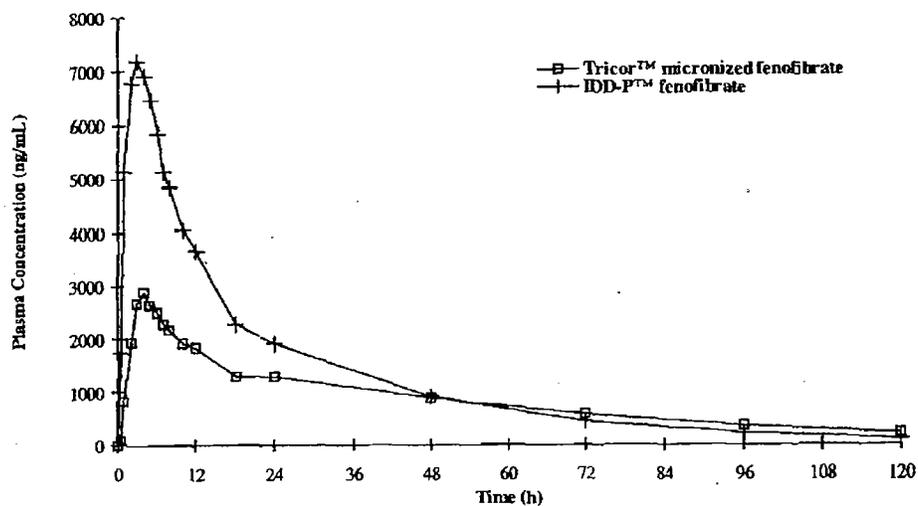
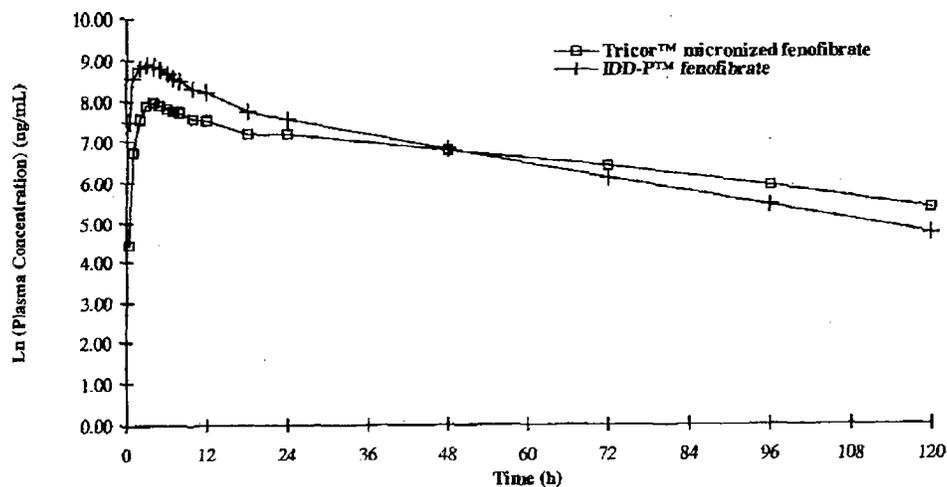


Figure 2 Fenofibric Acid Ln (Mean Concentration)- (Time profile; N = 20)



1. Title page

Title: Comparative bioavailability study of IDD-PTM fenofibrate in healthy subjects: one 160 mg tablet versus three 50 mg tablets.

Test drug: IDD-PTM fenofibrate tablet 160 mg and IDD-PTM fenofibrate tablet 50 mg x 3

Indication: This was a single center, open-label, randomized, 2-way crossover study to compare the bioavailability of three tablets of IDD-PTM fenofibrate 50 mg versus one tablet of IDD-PTM fenofibrate 160 mg under low-fat fed conditions. Doses were separated by a washout period of 9 days 23 hours and 30 minutes.

Sponsor's name and address: RTP Pharma Inc., 1000 chemin du Golf, Verdun, Quebec, Canada, H3E 1H4
Contact: _____

Study number(s): _____

Development phase: Phase I pharmacokinetic study

Study dosing dates: October 5, 2001 – October 15, 2001
Study Completion Date: November 8, 2001

Investigator(s): _____

Investigator: _____

Date: December 12, 2001

Confidentiality statement: This document is strictly confidential. It was developed for RTP Pharma Inc. and should not be disclosed to a third party, with the exception of regulatory agencies and study audit personnel. Reproduction, modification, or adaptation, in part or in total, is strictly forbidden without prior written approval by RTP Pharma Inc.

Project No. FEN100-C12 / 01270

Comparative Bioavailability Study of IDD-PTM Fenofibrate In Healthy Subjects: one 160 mg tablet versus three 50 mg tablets

Methodology:

This was a single-center, single dose, open-label, randomized, two-treatment, two-period, two-sequence crossover study to compare the bioavailability of three tablets of IDD-PTM fenofibrate 50 mg versus one tablet of IDD-PTM fenofibrate 160 mg under low-fat fed conditions. Doses were separated by a washout period of 9 days 23 hours 30 minutes. Twenty-four (24) healthy, adult (13 males and 11 females) non-smokers (for at least 3 months) were enrolled in this study. Subjects were confined from late afternoon on the day prior to dosing, until after the 24.0-hour post-dose blood draw in each period.

Subjects were administered 1 tablet of IDD-PTM fenofibrate 160 mg (Treatment A) or 3 tablets of IDD-PTM fenofibrate 50 mg (Treatment B) after a supervised overnight fast of at least 9.5 hours and subsequent consumption of a low-fat test meal. This meal was consumed over an interval of 25 minutes and was completed 5 minutes prior to study drug administration.

All blood samples were drawn into blood collection tubes (1 x 7 mL) containing EDTA, prior to drug administration and 0.500, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 18.0, 24.0, 48.0, 72.0, 96.0, and 120.0 hours post-dose, in each period. All blood samples were collected via direct venipuncture.

Blood samples were centrifuged at 3,000 rpm for 10 minutes at approximately 4°C. Two aliquots of at least 1.2 mL of plasma were dispensed into polypropylene tubes as soon as possible, before being transferred to a -20°C±5°C freezer, pending analysis.

Number of Subjects (planned and analyzed):

A total of 24 healthy, adult non-smokers (13 males and 11 females) were dosed in both periods. Two (2) subjects (one female subject [Subject No. 20] and one male subject [Subject No. 22]) were considered as not having completed the clinical portion of the study because blood samples could not be obtained for three consecutive timepoints. Therefore, 22 (12 males and 10 females) of the 24 subjects were considered as having completed the clinical portion and their data were used for the pharmacokinetic analysis. Safety analysis and procedures were performed for the 24 subjects who were dosed.

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Inclusion and Exclusion Criteria:

Inclusion Criteria:

- 18 to 55 years old;
- weight within $\pm 20\%$ of the ideal body weight of the Metropolitan Insurance Company scale;
- deemed "normal" following a comprehensive clinical assessment (detailed medical history, complete physical examination, and ECG) and laboratory investigations (hematology, biochemistry, urinalysis), the results of which must be within the normal range and/or clinically acceptable for healthy subjects;
- non-smoker, non-tobacco user for at least 3 months;
- negative urine drug screen and alcohol urine or breath test;
- female subjects had to have a negative pregnancy test at screening. Over the course of the study, females had to practice a method of contraception with greater than 90% reliability, or be sterile or post-menopausal;
- subjects with "normal" dietary habits (i.e., no restrictive regimen) and willing to eat the test meal;
- informed subjects accepting the study constraints and restrictions and having signed the informed consent.

Exclusion Criteria:

- history of major medical/psychiatric illness or surgery which, in the judgement of the Investigator, puts the subject "at risk" or is likely to modify his handling of the study drug;
- suffering from any acute or chronic systemic disease or disorder;
- history of hypersensitivity or intolerance to fibrate drugs;
- regular use of sedatives, hypnotics, tranquilizers or any other addictive substances;
- signs, symptoms, and laboratory test values outside the clinically acceptable "normal range" for healthy subjects;
- history or evidence of acute or chronic alcohol abuse (>14 drinks per week);
- excessive consumption (> 5 cups/day) of tea, coffee, chocolate, and/or other xanthine-containing food or beverages;
- positive HIV or HCV test, and/or a positive HBsAg test;
- received blood or plasma derivatives in the year preceding the initiation of the study;
- plasma donation in the 7 days preceding the initiation of the study and blood donation in the 56 days preceding the initiation of the study or intention to make blood or plasma donation during the study or within the three months following the study completion;
- pregnant or lactating;
- drug treatment during the two weeks preceding the study, except for women who could continue taking appropriate birth control medication;
- drug treatment that could lead to induction of hepatic microsomal enzymes (e.g., carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin) within 3 months of the study start;
- subject who had participated in another clinical study of any kind (drug or device) in the month immediately prior to the start of this study;
- subject who, in the judgement of the Investigator, was likely to be non-compliant or uncooperative during the study;
- subject who had forfeited his freedom by administrative or legal award or who was under guardianship;
- subject who could not be contacted in case of emergency.

Project No. FEN100-C12 / 01270

Comparative Bioavailability Study of IDD-PTM Fenofibrate In Healthy Subjects: one 160 mg tablet versus three 50 mg tablets

Test Product (name, dose, lot/batch number, expiry/reassay date, potency, administration):

IDD-PTM fenofibrate, RTP Pharma Inc., Canada; lot number: 003; reassay date: 2002/03; potency: [redacted] /tablet; administered as a 1 x 160 mg tablet (Treatment A).

IDD-PTM fenofibrate, RTP Pharma Inc., Canada; lot number: 001; reassay date: 2002/02; potency: [redacted] /tablet; administered as 3 x 50 mg tablets (Treatment B).

Duration of Treatment:

Subjects were given either IDD-PTM fenofibrate 1 x 160 mg tablet or IDD-PTM fenofibrate 3 x 50 mg tablets under low-fat fed conditions. Subjects were confined to the clinical facility from at least late afternoon on the day prior to dosing, until after the 24.0-hour post-dose blood draw, in each period. Clinical procedures (return visits to the clinical facility) extended until approximately 120.0 hours post-dose.

Criteria for Evaluation:

Pharmacokinetics/Bioavailability:

The following pharmacokinetic parameters were calculated for fenofibric acid: AUC_{0-1} , $AUC_{0-\infty}$, C_{max} , % extrapolated, t_{max} , k_{el} , $t_{1/2}$, and F_{rel} .

Primary parameters: AUC_{0-1} , $AUC_{0-\infty}$ and C_{max} .

Secondary parameters: % extrapolated, t_{max} , k_{el} , $t_{1/2}$ and F_{rel} .

Safety:

Vital signs (respiratory rate and oral temperature; blood pressure and pulse rate, after having been seated for at least 3 minutes) were performed for each subject during the evening prior to drug administration in Periods 1 and 2.

Throughout the study, subjects were monitored for adverse events. At the times of admission, subjects were asked a standard probe question concerning the onset of a new illness since the last visit, and at the time of discharge, each subject was asked how he/she was feeling.

An alcohol breath test and a urine drug screen were performed for each subject at the time of admission for Periods 1 and 2.

Pregnancy tests were performed at the time of screening, admission for Periods 1 and 2 and 4 to 9 days after the final blood collection. In error, a urine pregnancy test was performed at the time of screening (not a serum pregnancy test, as specified in the protocol). However, a serum pregnancy test was performed at the time of admission for Period 1 and subjects' eligibility was re-assessed based on these results. Urine pregnancy tests were performed at the time of admission for Periods 1 and 2 and 4 to 9 days after the final blood collection.

Laboratory tests (hematology, biochemistry, and urinalysis), physical examinations, and vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature) were performed between 4 and 9 days after the last blood draw of the last period.

Statistical Methods:

Descriptive statistics with means, standard deviations, coefficients of variations and range (min.) and (max.). ANOVA incorporating the gender effect performed on ln-transformed AUC_{0-4} , $AUC_{0-\infty}$ and C_{max} and untransformed t_{max} , k_{el} and $t_{1/2}$ at the alpha level of 0.05. Ratio of geometric least-squares means (B/A) and 90% geometric confidence interval around the ratio for ln-transformed AUC_{0-4} , $AUC_{0-\infty}$ and C_{max} .

Pharmacokinetic/Bioavailability Results:

Through the study there were no significant protocol deviations to confound the pharmacokinetics and bioavailability analyses. Study results were corrected for dose.

- Ratios (B/A) of least-squares means for AUC_{0-4} , $AUC_{0-\infty}$, and C_{max} were 96.53%, 96.23% and 97.36%, respectively, for uncorrected data, and 102.97%, 102.65% and 103.85%, respectively, for dose corrected data. These results demonstrate a comparable extent and rate of absorption of IDD-PTM fenofibrate tablet 50 mg x 3 (B) and IDD-PTM fenofibrate tablet 160 mg(A) and dose proportionality between the two formulations.
- ANOVA detected a statistically significant difference between treatments for ln-transformed AUC_{0-4} and $AUC_{0-\infty}$ and untransformed t_{max} .
- ANOVA also detected a statistically significant difference between genders for ln-transformed C_{max} and untransformed $t_{1/2}$ and k_{el} .

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Safety Results:

The Investigator judged the reported protocol deviations unlikely to have affected the results or the conclusions of the study.

Physical examinations, vital signs, ECGs, and laboratory tests were performed at the times specified in the protocol. Clinically significant abnormal post-study laboratory results were obtained for 4 subjects. Protein in urine was observed in Subject Nos. 05 and 11. Subject No. 09 had increased blood levels of glucose, AST, ALT, and creatine kinase and Subject No. 17 had increased creatine kinase levels. The tests were repeated and yielded normal or not clinically significant results. All other post-study laboratory test results and vital signs measurements were within normal limits or were judged to be not clinically significant by the Investigator.

Alcohol breath tests and urine drug screens were performed for each subject at the times specified in the protocol. Pregnancy tests were performed for all female subjects at the times specified in the protocol. All tests yielded negative results for all subjects.

A total of 37 adverse events occurred during the study: 1 adverse event occurred prior to Period 1 dosing and 36 occurred post-dose of either Period 1 or 2. The relationship to the study medication of the 36 post-dose adverse events can be broken down as follows: 2 adverse events were judged "probable", 13 were judged "possible", 5 were judged "remote", and 16 were judged "unrelated". The pre-dose adverse event was assessed as "unrelated" to the study medication. The severity at onset was mild for 22 adverse events and was moderate for 7 adverse events. The severity of the remaining 7 adverse events was not graded, as these events were associated with clinically significant post-study laboratory results. No serious, severe, or significant adverse events were reported.

The reported post-dose adverse events are summarized as follows:

Deaths:	None
Discontinuations from AEs:	None
Serious or severe AEs:	None
Probable-drug-related AEs:	Asthenia (2)
Possible-drug-related AEs:	Abdominal pain (1), back pain (2), creatine PK increase (2), headache (4), pain (2), AST increase (1), ALT increase (1)
Remote-drug-related AEs:	Pharyngitis (2), urinary tract infection (1), albuminuria (2)
Unrelated AEs:	Ecchymosis (5), headache (3), hyperglycemia (1), nausea (1), pain (1), pharyngitis (2), rhinitis (2), vasodilation (1)

Summary Conclusions:

Pharmacokinetic/Bioavailability:

Based on the least-squares means ratios (B/A) and 90% geometric confidence intervals of AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} that were within the 80% - 125% range for both the uncorrected and dose corrected data, it can be concluded that the extent and rate of absorption of IDD-PTM fenofibrate are comparable when administered as a 1 x 160 mg tablet or as 3 x 50 mg tablets. Therefore, dose proportionality between the two formulations had been demonstrated.

Safety:

All study treatments were well tolerated.

Project No. FEN100-C12 / 01270
Comparative Bioavailability Study of IDD-PTM Fenofibrate In Healthy Subjects: one 160 mg tablet versus three 50 mg tablets

Transfer of Obligations:

No obligations were transferred. RTP Pharma retains all obligations.

Contract research organizations assisted RTP Pharma with the following:

- Clinical site activities [REDACTED] Address: see above)
 - Ethics committee submissions
 - Study documentation (RTP Pharma prepared the protocol)
 - Study conduct
 - Clinical study report
- Analytical site activities [REDACTED] Address: see above)
 - Analytical assays
 - Statistical analyses
 - Analytical report

Financial Disclosure:

As per forms FDA 3455 and FDA 3454, there were no disclosable financial arrangements or interests between the study sponsor (RTP Pharma Inc.) and clinical study site personnel of [REDACTED] whereby the value of compensation to [REDACTED] could be influenced by the outcome of the study.

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Table 1. FEN100-C12. Summary of Pharmacokinetic Parameters for IDD-PTM Fenofibrate Tablet 160 mg lot #003 (A) and IDD-PTM Fenofibrate Tablet 50 mg x 3 lot #001 (B) Given under Low-fat Fed Conditions.

Parameters	IDD-PTM fenofibrate tablet 160 mg (A)			IDD-PTM fenofibrate tablet 50 mg x 3 (B)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC _{0-t} (ng·h/mL)	159854.20	38356.37	23.99	153455.66	35136.89	22.90
AUC _{0-∞} (ng·h/mL)	163053.19	39568.72	24.27	156125.97	36311.61	23.26
C _{max} (ng/mL)	12149.51	1308.99	10.77	11933.90	2462.90	20.64
% extrapolated (%)	1.92	0.95	49.61	1.63	0.89	54.38
t _{max} (h)	3.14	1.32	41.94	2.56	0.66	25.95
k _{el} (h ⁻¹)	0.0394	0.0106	26.87	0.0400	0.0111	27.82
t _{1/2} (h)	18.78	4.96	26.42	18.68	5.31	28.40
F _{rel} (vs A) (%)	-	-	-	96.30	6.68	6.94

Table 2. FEN100-C12. Summary of Treatment Comparisons (uncorrected) for IDD-PTM Fenofibrate Tablet 160 mg lot #003 (A) and IDD-PTM Fenofibrate Tablet 50 mg x 3 lot #001 (B) Given under Low-fat Fed Conditions.

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of Arithmetic Means ¹	Ratio of LS Means ²	90% Confidence Interval ³		Intra-Subject CV
				Lower	Upper	
AUC _{0-t}	IDD-PTM fenofibrate tablet 50 mg x 3 (B) vs IDD-PTM fenofibrate tablet 160 mg (A)	96.00%	96.53%	93.92%	99.22%	5.25%
AUC _{0-∞}	IDD-PTM fenofibrate tablet 50 mg x 3 (B) vs IDD-PTM fenofibrate tablet 160 mg (A)	95.75%	96.23%	93.76%	98.77%	4.98%
C _{max}	IDD-PTM fenofibrate tablet 50 mg x 3 (B) vs IDD-PTM fenofibrate tablet 160 mg (A)	98.23%	97.36%	91.29%	103.84%	12.35%

¹ Calculated using arithmetic means (untransformed data).
² Calculated using least-squares means (ln-transformed data).
³ 90% Geometric confidence interval based on ln-transformed data

Table 3. FEN100-C12. Summary of Treatment Comparisons (dose corrected) for IDD-PTM Fenofibrate Tablet 160 mg lot #003 (A) and IDD-PTM Fenofibrate Tablet 50 mg x 3 lot #001 (B) Given under Low-fat Fed Conditions.

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of LS Means ¹	90% Confidence Interval ²	
			Lower	Upper
AUC _{0-t}	IDD-PTM fenofibrate tablet 50 mg x 3 (B) vs IDD-PTM fenofibrate tablet 160 mg (A)	102.97%	100.18%	105.83%
AUC _{0-∞}	IDD-PTM fenofibrate tablet 50 mg x 3 (B) vs IDD-PTM fenofibrate tablet 160 mg (A)	102.65%	100.01%	105.36%
C _{max}	IDD-PTM fenofibrate tablet 50 mg x 3 (B) vs IDD-PTM fenofibrate tablet 160 mg (A)	103.85%	97.37%	110.77%

¹ Calculated using least-squares means (ln-transformed data).
² 90% Geometric confidence interval based on ln-transformed data

Figure 1 Fenofibric Acid Mean Concentration - (Time profile; N = 22)

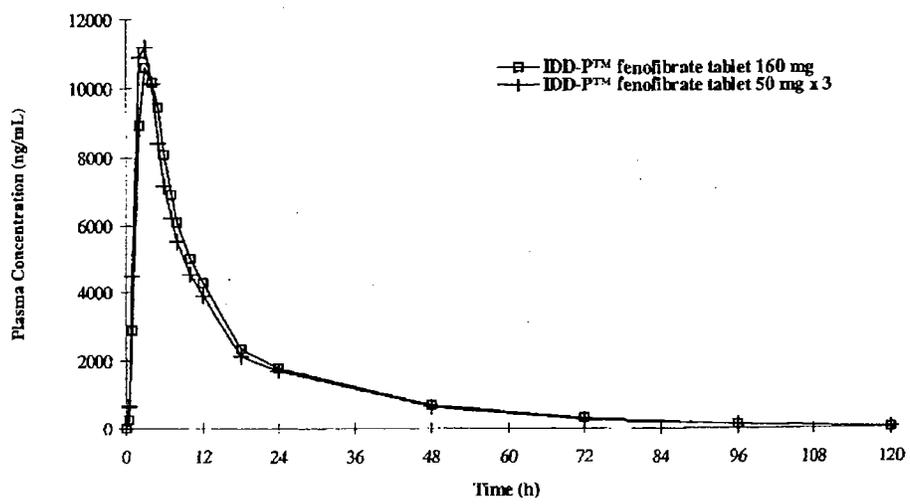
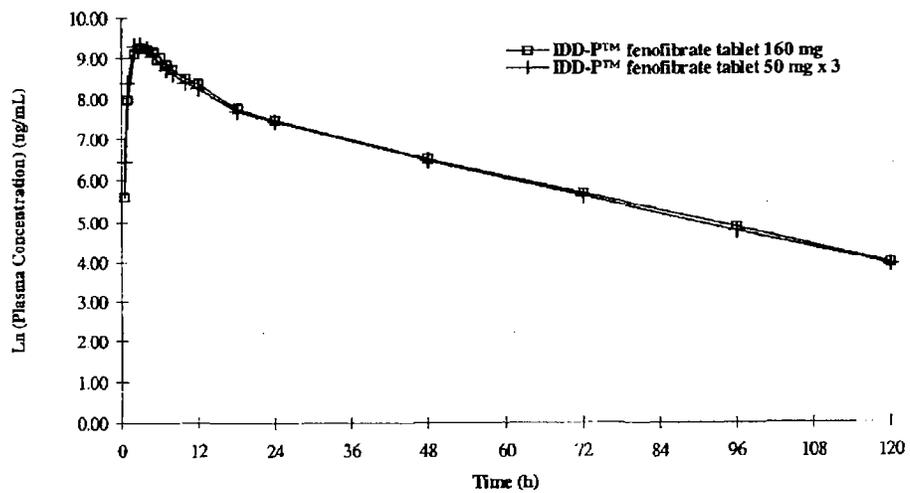


Figure 2 Fenofibric Acid Ln (Mean Concentration)- (Time profile; N = 22)



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/s/

Wei Qiu
3/11/02 02:06:34 PM
PHARMACOLOGIST

Hae-Young Ahn
3/11/02 06:35:18 PM
BIOPHARMACEUTICS

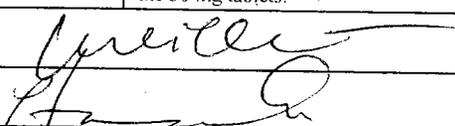
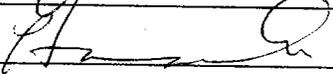
Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

Information		Information	
NDA Number	21-350	Brand Name	IDD-P (Fenofibrate) Tablets
OCPB Division (I, II, III)	II	Generic Name	Fenofibrate
Medical Division	510	Drug Class	Lipid lowering
OCPB Reviewer	Wei Qiu, Ph.D.	Indication(s)	Hypertriglyceridemia (Fredrickson Types IV and V)
OCPB Team Leader	Hae-Young Ahn, Ph.D.	Dosage Form	Tablet
		Dosing Regimen	160 mg and 50 mg
Date of Submission	25 Jun 01	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	RTP Pharma
PDUFA Due Date		Priority Classification	
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	x			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				

alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	2		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	No.	<p>Neither dose proportionality study nor clinical study was conducted on the 50 mg tablet.</p> <p>Since the sponsor has not established dose proportionality and the dissolution profiles for 160 mg and 50 mg strengths were different, the bio waiver request for the 50 mg strength can not be granted.</p> <p>To make this NDA filable, the sponsor is recommended to conduct either a BE study to compare the 50 mg IDD-P™ with the 67 mg Tricor® capsule or a dosage form equivalence study to compare one 160 mg tablet with three of the 50 mg tablets.</p>		
Primary reviewer Signature and Date	 8/9/01			
Secondary reviewer Signature and Date	 8/9/01			

CC: NDA 21-350, HFD-850(Electronic Entry or Lee), HFD-510(Koch), HFD-870(Ahn, Malinowski, Hunt).

RTP Pharma Inc. (RTP Pharma) submitted NDA 21-350 under 505(b)(2) for Insoluble Drug Delivery-Microparticle (IDD-P™) fenofibrate tablets (160 mg and 50 mg strengths) to treat hyperlipidemia Type IV and V. The sponsor claimed that IDD-P™ provided increased bioavailability and no significant food effect on extent of absorption. In the proposed labeling, the sponsor indicated that for adult patients with hypertriglyceridemia, the initial dose is 50 mg to 160 mg per day.

Since no clinical trial has been conducted to support safety and efficacy, the approval of this NDA would be based on literature information and bioequivalent studies comparing with fenofibrate Reference List Drug (RLD) Tricor® capsule. Section 6 included a summary of pharmacokinetic data from the RLD and literature information for fenofibrate through January 2001.

In addition, Section 6 also contained BE studies (FEN100-C04A and FEN100-C06) comparing 160 mg IDD-P™ and 200 mg Tricor capsule. In order to support the marketing of the 50 mg strength, in Pre-NDA meeting the sponsor proposed to conduct dose proportionality study and in vitro dissolution testing in lower dose strength(s). On the basis of these results a Biowaiver Request would be submitted. In response, Dr. Ahn indicated that if the drug product is proportionally similar in its active and inactive ingredients, an in-vivo bioequivalence determination of lower strength(s) can be waived based upon dissolution tests and linear pharmacokinetics. Since no dose proportionality study has been conducted, the linear pharmacokinetics was not established. Moreover, the in vitro dissolution testing showed that the dissolution profiles for the 160 mg and 50 mg strengths were not similar ($F_2 = \text{---}$ the complete study report was not included). Although the drug product is proportionally similar in its active and inactive ingredients, the Biowaiver request can not be granted to the 50 mg strength. Therefore, the sponsor is recommended to conduct a BE study comparing the 50 mg IDD-P™ and 67 mg Tricor® capsule.

In summary, this NDA is not filable.

The following studies were included in Section 6.

1. FEN100-C10---Pharmacokinetic study of the Influence of Fat from Food on the Bioavailability of Micronized Fenofibrate in Healthy Subjects
2. FEN100-C11---Pilot Study of the Food Effect on the Bioavailability of Microcoated Fenofibrate in Healthy Subjects and Comparison with Micronized Fenofibrate under Fasting Conditions

3. FEN100-C03---Pilot Study of the Food Effect on the Bioavailability of IDD-P Fenofibrate in Healthy Subjects (Part 1) and Comparison with Micronized Fenofibrate under Low-fat Fed Conditions (Part 2)
4. FEN100-C04A---Comparative Bioavailability of IDD-P Fenofibrate Tablet 160 mg and Fenofibrate Microcoated Tablet 160 mg with Micronized Fenofibrate Capsule 200 mg in Healthy Subjects
5. FEN100-C05---Comparative Bioavailability of IDD-P Fenofibrate Tablet 160 mg under Fasting, Low-fat, and High-fat Fed Conditions in Healthy Subjects
6. FEN100-C06---Comparative Bioavailability of IDD-P Fenofibrate Tablet 160 mg with Micronized Fenofibrate Capsule 200 mg in Healthy Fed Subjects.