CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-986

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-986 APPLICANT:Martec Scientific

DRUG PRODUCT:Diclofenac Sodium Delayed-Release
75 mg and 50 mg Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

Diclofenac Sodium
75 mg Delayed-Release Tablet
50 mg Delayed-Release Tablet
Reviewer: Andre Jackson
ANDA # 74-986
WP# 74986A.598

Martec Scientific
Kansas City, Mo.
Submission Date:
May 29, 1998

REVIEW OF AN AMENDMENT TO A BIOEQUIVALENCE STUDY

Introduction

The firm submitted a study on June 10, 1997 for their 75 mg and 50 mg delayed-release tablets. The studies were found to be unacceptable. A reply to these deficiencies was submitted by the firm on November 11, 1997. This amendment was reviewed by the Division of Bioequivalence and a second deficiency letter was issued since the 50 mg fasting and 75 mg food studies were unacceptable when subjects with the first time point as Cmax were deleted from the population. Subsequently a teleconference was held between the firm and the Division of Bioequivalence at which time it was decided that all Cmax values would be included in the data analysis since diclofenac is a delayed-release product. The firm agreed to resubmit the data including an analysis for all of the data.

Deficiency 1.

Page(s) 4

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Recommendation:

1. The fasting bioequivalence study submitted by Martec on June 10, 1997 on its 75 mg diclofenac tablet, Lot No. LT4961 was found to be acceptable on 9/30/97. The current fasting bioequivalence study conducted by Martec on its 50 mg diclofenac tablet, Lot No. 960103, and the food study on the 75 mg diclofenac tablet, Lot No. 960105, comparing them to Ciba Geigy's Voltaren 50 mg tablet

Lot No. LT401 and Voltaren 75 mg tablet Lot No. LT4961 respectively, have been found to be acceptable by the Division of Bioequivalence.

2. The dissolution testing conducted by Martec on the 75 mg strength, Lot No. 960105 and the 50 mg strength Lot No. 960103 has been found to be acceptable.

3. The <u>in vitro</u> dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCL at 37 C using USP 23 apparatus II paddles at 50 rpm. for 2 hours followed by dissolution in 900 ml phosphate buffer, pH 6.8 for 45 minutes. The test product should meet the following specifications:

Andre J. Jackson /S/
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG /S/ Date: 9/28/98

Concur: /S/ Date: 10/5/98
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

Comparative Dissolution

Test Substance:Diclofenac Na Delayed-release 50mg Tablets
QC96962 Lot 960103

Reference Substance.Voltaren 50mg Tablets
QC96484 Lot LT4101

Test Conditions:900 mL of pH 6.8 Buffer (Not Deaerated) at 37 degrees C with Paddles at 50 RPMs

NOTE:,The following tables show only the *Buffer* portion of the dissolution analysis

	Test Substance Percent Found / Label						Reference Substance Percent Found / Label					
	5 Min.	10 Min.	20 Min.	30 Min.	45 Min.	60 Min.	5 Min.	10 Min.	20 Min.	30 Min.	45 Min.	60 Min.
Avg.	17.03	74.2	89.7	90.5	91.9	92.64	0.31	30.7	78.0	84.8	86.81	87.9
SD	21.4	18.2	9.8	9.8	8.6	7.78	0.48	12.8	3.33	3.01	2.8	2.6
Range												
High												
Rang·												
Low												

Comparative Dissolution

Test Substance: Diclofenac Na Delayed-release 75mg Tablets
QC96965 Lot 960105

Reference Substance. Voltaren 75mg Tablets
QC96485 Lot LT4961

Test Conditions:900 ml of pH 6.8 Buffer at 37 degrees C with Paddles at 50 RPMs

NOTE: The following tables show only the *Buffer* portion of the dissolution analysis

Dissolution	Test Substance Percent Found/Label						Reference Substance Percent Found/Label					
	5 Min.	10 Min.	20 Min.	30 Min.	45 Min.	60 Min.	5 Min.	10 Min.	20 Min.	30 Min.	45 Min.	60 Min.
Avg.	6.82	39.3	79.6	83.6	84.6	86.1	0.69	18.4	74.3	85.9	88.7	89.7
SD	12.6	31.8	13.3	11.3	10.1	9.33	0.86	11.8	10.3	2.9	2.4	2.4
Ran												
High												
Range												
Low												

BIOAVAILABILITY

MARTEC
SCIENTIFIC, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

BIOEQUIVALENCY AMENDMENT – ANDA 74-986

May 29, 1998

ORIG AMENDMENT
N/AB

Mr. Douglas Sporn
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600
7500 Standish Place
Rockville, MD 20855

RE: **BIOEQUIVALENCY AMENDMENT** to Pharmacokinetics Section – ANDA 74-986 – Diclofenac sodium Delayed-release tablets, 50 mg and 75 mg.

Dear Mr. Sporn:

In accordance with 21 CFR 314.96, Martec Scientific is herewith filing an amendment to ANDA 74-986 for Diclofenac delayed-release tablets 50 mg and 75 mg in response to the deficiency letter of March 24, 1998 from the division of bioequivalence.

As required a copy of the letter of March 24, 1998 is included (**APPENDIX I**) and all the comments in the letter are addressed in the order in which they appear (**APPENDIX II**).

An archival copy and a review copy are provided.

Sincerely,

Paul T. Sudhakar

Paul T. Sudhakar
President/COO

Enclosures

1. **Division of Bioequivalence deficiency letter of March 24, 1998 (APPENDIX I)**
2. **Firms response to the deficiency letter (APPENDIX II**

RECEIVED
JUN 0 1 1998
GENERIC DRUGS

MAR 24 1998

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BIOEQUIVALENCY DEFICIENCIES

ANDA 74-986 APPLICANT:Martec Scientific

DRUG PRODUCT:Diclofenac Sodium

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

The guidance issued by the Division of Bioequivalence and which you followed is a recommendation issued to assist investigators. However, following the procedures in the guidance is no guarantee of success for your product since products do vary.

Whenever a product exhibits a Cmax prior to the scheduled 15 min time sample protocols have been approved with sampling as early as 5 minutes so that contrary to your statement there is no ethical concern related to 5 minute sampling.

Unfortunately there is no single scientific justification for the Division's decision as you requested but the sum total of the statements in our response provides a rationale for our decision.

6. The dissolution data that you presented is unacceptable since you did not develop a dissolution profile for the products.

Sincerely yours,

/S/

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

Diclofenac Sodium
75 mg Delayed-Release Tablet
50 mg Delayed-Release Tablet
ANDA # 74-986
Reviewer: A.J. Jackson
WP # 74986A.N97

Martec Scientific
Kansas City, Mo.
Submission Date:
November 11, 1997

Review of Amendment To Fasting Bioequivalence Studies for 75 mg and 50 mg Tablets and a Post-Prandial Study for 75 mg Tablet and Dissolution Data

Introduction

The firm submitted a study on June 10, 1997 for their 75 mg and 50 mg delayed-release tablets. The studies were found to be unacceptable and the current submission contains the firm's reply to the deficiencies.

Deficiency 1.

1.Starting clinical and analytical dates were not clearly stated by the firm for the 75 mg fasting, 50 mg fasting and 75 mg post-prandial studies.

Firm's Response:

On page 7 in attachment 1 the firm lists the information on clinical and analytical starting dates.

FDA Reply:
The firm's response is acceptable.

Deficiency 2.

2.Expiration dates for the reference formulation Lot numbers LT4961 and LT4101 were not presented. Also the lot sizes for 960105 and 960103 for the test drug were not presented.

Firm's Response:

On page 000281 in attachment 1a the firm lists the information on expiration dates and lot sizes not given in the original review.

FDA Reply:

The firm's response is acceptable.

Deficiency 3.

3.The overall organization of the ANDA was poor and difficult to follow. Finding required study information was difficult and time consuming. In the future the firm should organize the submission by having everything related to a particular dosage strength within the same volume. Also label the tabs according to the contents of that section instead of using designations such as modules and attachments. This organizational structure is very confusing.

Response

We agree that the ANDA should be organized to minimize review time and to assist the reviewer in quickly locating the information. We have filed two more ANDAs in this format with some changes. However, future ANDAs submitted by this firm will use the FDA recommended format.

FDA Reply:

The firm's response is acceptable.

Deficiency 4.

4.The protocols for the 75 mg fasting, 50 mg fasting and 75 mg post-prandial studies used smokers. However, it was not clear if they were allowed to smoke during the study. The firm needs to clarify this point.

Response

Subjects who did not smoke more than 10 cigarettes per day were allowed to participate in the three studies. However, from the evening prior to drug intake until the last blood sample at 12 hours after drug administration, smoking was not allowed (a copy of

Section 2.2.5. of the reports, is enclosed as *attachment 2)*.

FDA Reply:

The firm's response is acceptable.

Deficiency 5.

5.The firm should explain the rationale for preparing calibration samples by merely adding together the required volumes as presented in their protocol instead of preparing them volumetrically (ie.,using volumetric containers).

Response

The calibration samples were prepared volumetrically using calibrated volumetric flasks. As is stated in the analytical report (page 11 of all three reports is added as *attachment* 3) blank plasma was added to obtain the required volume.

FDA Reply:

The Division of Bioequivalence agrees with the firm that your calibrators were prepared volumetrically as you stated. However, it appears that the working solutions for calibration samples (eg,pg 11/30 Vol 3.1) were prepared by adding water to your stock. Furthermore some of your final volumes were 2.5 ml which is a non-traditional final volume. You should explain the preparation of these working solutions in detail.

Deficiency 6.

6.The firm did not supply summary statistics for each calibration curve and information on the amount added and found so that assay precision could not be evaluated.

Response

The method validation report on pages A7/A20-A8/A20 (enclosed *as attachment -4)* supplied as an appendix to the analytical report to study 96-802 contains the summary statistics of the calibration curves run on -both systems (including the

amounts added and found.

FDA Reply:
The data provided by you is pre-assay validation data. The requested data is that which was collected during subject sample processing. It is the data which supports the QC data presented on page 00446(21/30) Vol. 3.1 in the original submission. The data should be presented for each study in the same format as the QC data.

Deficiency 7.

7.The firm should explain why Table 2 page A7/A20 in volume 3.5 presented under CPR 96-802 the 75 mg study has the table legend for 96-801 which is the 50 mg study?

Response

In study 96-801, the analytical method was validated on system , whereas in study 96-801 both and were used. Therefore, the validation results for obtained in study 96-801 also appear in the report for study 96-802.

FDA Reply:

The firm's response is acceptable.

Deficiency 8.

8.The firm should explain why is there such a big difference in recovery between in their validation studies.

Response

Although both consists of the same analytical equipment and identical conditions exists, validation results, such as recovery, may differ between the systems. All validation runs for both systems were valid and within the preset ranges. Results of validation runs are presented on pages 21-22 of the analytical report of studies 96-801 and 96-802 and on page 20 of the analytical report of study 96-803 (copies of the corresponding pages are included as *attachment 5)*.

FDA Reply:

The data on pages A14/A20 and A15/A20 in Vol 3.5 indicate that there is a problem either with sample preparation or loss in one of the systems. For example for the 60 ng/ml sample the recovery for validation was 96% while for validation 3 at the same concentration it was 60%, indeed a large difference. The Division of Bioequivalence believes that your preset range and validation criteria need to be changed if they allow identical concentrations to be so different and still be acceptable. You need to supply more information on your assay acceptance criteria.

Deficiency 9.

9.The firm should explain why they did not prepare fresh standards for the freeze/thaw study as they did for the long term stability studies.

Response

In short-term stability tests (i.e. freeze/thaw stability) QC samples that were prepared freshly on the same day were used.

FDA Reply:

The firm's response is acceptable.

Deficiency 10.

10.The firm should explain why the 2 month long term stability data is almost 20% larger (absolute values) at 800 ng/ml and 30% larger for 60 ng/ml compared to the 1 month and 2 month samples.

Response

Based on experience, there is an intrinsic error in all procedures related to sample analysis (i.e. sample preparation and equipment) this error is about on average but could be higher on some occasions. Most importantly the data clearly showed that their was no stability problem.

FDA Reply:

The error which you report for the samples on pages A18/A20 and A19/A20 in Vol 3.5 seems high for the preparation of anlaytical samples. The experience of the Division of Bioequivalence indicates a much lower per cent of error(ie.,3-5%) unless the samples are unstable or bind to the preparation vessel. Errors of the magnitude which you describe indicate that there is some undetermined problem in either your method or sample preparation. These large errors raise questions related to the validity of the these stability data.

Deficiency 11.

11.The firm should explain why they presented data for only 3 months stability when some samples were stored as long as 120 days?

Response

To be on the safe side, a 5-month stability test was performed the results of which are included in Appendix 11 (enclosed as *attachment 6)*.

FDA Reply:

The quality of the data from this 5-month stability data raises more questions related to the conduct and outcome of the data presented under deficiency 10. The 5 month data is acceptable.

Deficiency 12.

12.The firm did not give the type or normality of the buffer used in the dissolution study.

Response

The normality of the buffer used in the biostudy was PH buffer.

FDA Reply:

The firm's response is acceptable.

Deficiency 13.

13.The firm did not describe the assay used in the dissolution study. Also the firm should use 900 ml of pH 6.8 phosphate buffer for their dissolution studies instead of to be consistent with the USP supplement #6.

Response

The dissolution method has been revised in accordance with USP 23 supplement #6 and the current stability, future stability testing and finished product release testing will be performed with this method. The test method and results from a most recent dissolution study and the comparative study results with ml are presented in *attachment* 7. The only difference between the old method and the current revision is the volume of the dissolution media mL in the old method and 900 mL in the revised method.

FDA Reply:
The firm's response is acceptable.

Deficiencies 14 and 15.

14.When the subjects in the 50 mg fasting study that had Cmax as their first measurable time point were excluded from the analysis of the data, the 90% confidence interval for Ln Cmax was 67.8-150.7% which is outside of the acceptable limits of of the reference.

15.Deletion of subjects in the 75 mg food study that had Cmax as their first measurable time point resulted in ratios of geometric means for LnCmax of 73.5% which is outside the acceptable limits of

Response

The brand product Voltaren Delayed-Release Tablets are enteric coated tablets. The pharmaceutical formulation resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH environment in the duodenum. On average, peak plasma levels are achieved in 2 hours (range 1-4 hours) in fasting normal volunteers. When the product is taken with food there is usually a delay in the onset of absorption, of 1 to 4.5 hours, with

delays as long as 10 hours in some subjects.

The data (Physician's Desk Reference, 1995) indicates that diclofenac after administration of delayed release tablets is quickly absorbed (once released) and that in several subjects the first measurable plasma concentration can be Cmax. This very steep increase in the plasma concentration versus time profile, which is inherent to the product, makes the exact determination of the true absorption phase extremely difficult.

If, by chance, an additional sample taken earlier with a lower concentration above LOQ had been available, this subject's Cmax,. now deleted would have been included into the statistical evaluation.

It is also possible that, because of the rapid absorption, the true Cmax occurred just before the presently measured peak concentration. However, it is also possible that the "true" Cmax. occurred after the available peak concentration, because of very short distribution and elimination phase.

Ideally, blood sampling at 5-minute intervals could be considered, however, this still rules out the existence of a still higher plasma concentration and, in addition, would not be practically feasible due to ethical considerations. Martec adhered strictly to the OGD bioequivalence guidance available at that time. The sampling frequency used in the study was based on the standard protocol of the FDA available at the time of the study.

Furthermore, we believe that deletion of the subjects with Cmax values as the first point above LOQ would weaken the-study-scientifically, and therefore, these subjects should be included into the bioequivalence testing for Cmax.
For the above reasons, we feel that the data for these subjects should not be deleted and our bioequivalence study should be evaluated with inclusion of the subjects whose Cmax occurs at the first measurable plasma concentration. However, if you disagree with "Our comments", we would appreciate a scientific justification rather than a general statement, which might assist us in determination of our future course of action.

FDA Reply:

You state "The data (Physician's Desk Reference, 1995) indicates that diclofenac after administration of delayed release tablets is quickly absorbed (once released) and that in several subjects the first measurable plasma concentration can be Cmax." Since any reference to labeling should refer to current labeling, the 1998 version of the PDR (page 1831)was consulted and does not support your statement related to the first concentration being Cmax.

The problem is to clearly eliminate all other values as possible Cmax when one has an infinite possibilities as you have described. In the experience of the Division of Bioequivalence elimination of the subjects with an undefined Cmax is only harmful to the study outcome when the N is significantly decreased or the products are marginally bioequivalent. Your 75 mg product had those subjects with the first time point as Cmax deleted and still met the criteria.

The guidance issued by the Division of Bioequivalence is a recommendation issued to assist investigators. However, following the procedures in the guidance is no guarantee of success for your product since products do vary.

Whenever a product exhibits a Cmax prior to the scheduled 15 min time sample protocols have been approved with sampling as early as 5 minutes so that contrary to your statement there is no ethical concern related to 5 minute sampling.

Unfortunately there is no single scientific justification for the Division's decision as you requested but the sum total of the statements in our response provides a rationale for our decision.

Deficiency 16.

16. The firm should explain why they included the data for subject #32 in the analysis of their 50 mg study but it was not included on the data diskette submitted to the Division of Bioequivalence. Also why this subject's data analyzed since he exhibited an adverse effect? The firm should also explain what "prematurely withdrawn from the study due to an adverse event" means with respect to subject 32.

Response

Due to the occurrence of a syncope prior to *the* second drug administration (a copy of Section 3.4.3. is included as *attachment 8)* subject 32 withdrew his informed consent. The blood samples of subject 32 were not analyzed and, therefore, no data for this subject were included on the diskette submitted to the Division of Bioequivalence. This subject was thus excluded from the pharmacokinetic analysis. However, since he did receive test medication, subject 32 was included in the safety analysis.

FDA Reply:

The firm's response is acceptable.

Deficiency 17.

17.The firm should not have deleted subjects that have complete plasma profiles for the post-prandial (i.e.,Method III) study since the analysis of the data by LSMEANS accounts for the unbalanced study design and calculates appropriately weighted mean parameter value.

Response
The reviewer is correct in stating that LSMEANS accounts for unbalanced study designs. Method III was only performed to explore whether marked differences would appear in comparison to methods I and II(a copy of Section 3.3. of the report CPR 96-803 -is included as attachment 9). As presented in Table V (page 31, *attachment 9)* the same conclusion, i.e. no food effect, was drawn independent of the method used.

FDA Reply:

The firm's response is acceptable.

Deficiencies:

The dissolution data presented by the firm is unacceptable since they did not develop a dissolution profile for the products.

Recommendation:

The fasting bioequivalence study conducted by Martec on its 75 mg

diclofenac tablet, Lot No. 960105, comparing it to Ciba Geigy's Voltaren 75 mg tablet Lot No. LT4961 has been found to be acceptable by the Division of Bioequivalence. The bioequivalence studies conducted by Martec on its 50 mg diclofenac tablet, Lot No. 960103 and the food study on the 75 mg diclofenac tablet, Lot No. 960105, comparing them to Ciba Geigy's Voltaren 50 mg tablet Lot No. LT401 and Voltaren 75 mg tablet Lot No. LT4961 respectively, have been found to be unacceptable by the Division of Bioequivalence. Therefore, the overall application is found to be unacceptable to the Division of Bioequivalence.

2.The dissolution testing conducted by Martec on the 75 mg strength, Lot No. 960105 and the 50 mg strength Lot No. 960103 has been found to be incomplete.

/S/

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

Date: 3/13/98

Concur: /S/ Date: 3/18/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table 1 . In Vitro Dissolution Testing

Drug (Generic Name):Diclofenac
Dose Strength:75 mg and 50 mg
ANDA No.:74-986
Firm:Martec
Submission Date:November 11, 1997
File Name:74986A.N97

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 50
No. Units Tested: 12
Medium: 0.1 N HCL
PH 6.8 Phospahte buffer
Volume:900 ml
900 ml
Specifications:

Reference Drug: Voltaren
Assay Methodology:

Results of In Vitro Dissolution Testing: Acid

Sampling Times Minutes	Test Product Lot # 960103 Strength(mg) 50			Reference Product Lot # LT4101 Strength(mg) 50		
	Mean %	Range	%CV	Mean %	Range	%CV
120	0.01		346	0.57	--	19.2

Sampling Times Minutes	Test Product-Buffer Lot # 960103 Strength(mg) 50			Reference Product Lot # LT4101 Strength(mg) 50		
	Mean	Range	%CV	Mean	Range	%CV
45	92.29		5.3			

Sampling Times Minutes	Test Product-Acid Lot # 960105 Strength(mg) 75(Acid)			Reference Product Lot # LT4961 Strength(mg) 75(Acid)		
	Mean	Range	%CV	Mean	Range	%CV
120	0.31		25	0.20	7	29

Sampling Times Minutes	Test Product-Buffer Lot # 960105 Strength(mg) 75			Reference Product Lot # LT4961 Strength(mg) 75		
	Mean	Range	%CV	Mean	Range	%CV
45	89.03	1	9			

BIOEQUIVALENCY DEFICIENCIES

ANDA 74-986 APPLICANT:Martec Scientific

DRUG PRODUCT:Diclofenac Sodium

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

1. The Division of Bioequivalence agrees with you that your calibrators were prepared volumetrically as you stated. However, it appears that the working solutions for calibration samples (eg,pg 11/30 Vol 3.1) were prepared by adding water to your stock. Furthermore some of your final volumes were which are non-traditional final volumes. You should explain in detail the preparation of these working solutions.

2. The data provided by you is pre-assay validation data. The requested data is that which was collected during subject sample processing. It is the data which supports the QC data presented on page 00446(21/30) Vol. 3.1 in the original submission. The data should be presented for each study in the same format as the QC data.

3. Your data on pages A14/A20 and A15/A20 in Vol 3.5 indicate that there is a problem either with sample preparation or loss in one of the systems. For example, for the 60 ng/ml sample the recovery for validation was 96% while for validation 3 at the same concentration it was 60%, indeed a large difference. The Division of Bioequivalence believes that your preset range and validation criteria need to be changed if they allow identical concentrations to be so different and still be acceptable. You need to supply more information on your assay acceptance criteria.

4. The error which you report for the samples on pages A18/A20 and A19/A20 in Vol 3.5 seems high for the preparation of anlaytical samples. The experience of the Division of Bioequivalence indicates a much lower per cent of error (ie.,3-5%) unless the samples are unstable or bind to the preparation vessel. Errors of the magnitude which you describe indicate that there is some undetermined problem in either your method or sample preparation. These large errors

raise questions related to the validity of the these stability data.

5. You state "The data (Physician's Desk Reference, 1995) indicates that diclofenac after administration of delayed release tablets is quickly absorbed (once released) and that in several subjects the first measurable plasma concentration can be Cmax." Since any reference to labeling should refer to current labeling, the 1998 version of the PDR (page 1831)was consulted and does not support your statement related to the first concentration being Cmax.

   The problem is to clearly eliminate all other values as possible Cmax when one has an infinite possibilities as you have described. In the experience of the Division of Bioequivalence elimination of the subjects with an undefined Cmax is only harmful to the study outcome when the N is significantly decreased or the products are marginally bioequivalent. Your 75 mg product had those subjects with the first time point as Cmax deleted and still met the criteria.

   The guidance issued by the Division of Bioequivalence and which you followed is a recommendation issued to assist investigators. However, following the procedures in the guidance is no guarantee of success for your product since products do vary.

   Whenever a product exhibits a Cmax prior to the scheduled 15 min time sample protocols have been approved with sampling as early as 5 minutes so that contrary to your statement there is no ethical concern related to 5 minute sampling.

   Unfortunately there is no single scientific justification for the Division's decision as you requested but the sum total of the statements in our response provides a rationale for our decision.

6. The dissolution data that you presented is unacceptable since you did not develop a dissolution profile for the products.

Sincerely yours,

/S/

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

MARTEC
SCIENTIFIC, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

November 11, 1997

Mr. Douglas Sporn
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

BIOAVAILABILITY

RE: **Amendment** to Pharmacokinetics Section – ANDA 74-986 – Diclofenac sodium delayed-release tablets 50 mg and 75 mg.

Dear Mr. Sporn:

In accordance with 21 CFR 314.96, Martec Scientific is herewith filing an amendment to ANDA 74-986 for Diclofenac delayed-release tablets 50 mg and 75 mg, (See attachment FB 1 in response to the deficiency letter of October 17, 1997 from the division of bioequivalence.

As required a copy of the letter of October 17, 1997 is included and all the comments in the letter are addressed in the order in which they appear.

Sincerely,

Paul T. Sudhakar

Paul T. Sudhakar
President/COO

Enclosures

RECEIVED
NOV 12 1997
GENERIC DRUGS

OCT -5 1997

Diclofenac Sodium
75 mg Delayed-Release Tablet
50 mg Delayed-Release Tablet
ANDA # 74-986
Reviewer: A.J. Jackson
WP # 74986SD.697

Martec Scientific
Kansas City, Mo.
Submission Date:
June 10, 1997
June 26, 1997

Review of Fasting Bioequivalence Studies for 75 mg and 50 mg Tablets and Post-Prandial Study for 75 mg Tablet and Dissolution Data

Introduction

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID), advocated for use in painful and inflammatory rheumatic and non-rheumatic conditions. The anti-inflammatory activity of diclofenac, and most of its other pharmacological effects, are related to its inhibition of prostaglandin synthesis. Diclofenac is a potent inhibitor of cyclo-oxygenase, thereby decreasing the synthesis of prostaglandins, thromboxane and prostacyclin.

Mean plasma clearance of diclofenac in healthy subjects is 16 L/h, the mean elimination half-life is 1-2 hours. The area under the diclofenac plasma concentration versus time curve is linearly related to the dose in the dose range 25 - 150 mg and no accumulation occurs during repeated dosing. The drug is highly (>99%) bound to plasma proteins; its volume of distribution amounts to 0.12-0.17 L/kg body weight, suggesting distribution in the extracellular space. Diclofenac sodium is rapidly absorbed following oral administration with reported Tmax values of 1-3 hrs under fasting conditions. The reported Cmax ranged between 0.5-2 ug/ml. Area under the curve has been reported to increase linearly over the dose range 25-150 mg. Diclofenac sodium undergoes first-pass metabolism with a systemic availability of 50-60%.

Diclofenac sodium is currently marketed as Voltaren^{R} (Geigy) as 25, 50 and 75 mg triangular-shaped enteric-coated tablets.

OBJECTIVES

The purpose of the study is to investigate whether the new delayed release formulation of diclofenac-Na 75 mg (Ratiopharm GmbH/Martec Pharmaceutical, Inc.) is bioequivalent under fasting conditions to the reference formulation Voltaren 75 mg biconvex, triangular-shaped enteric-coated tablets(Ciba-Geigy).

Methods

The study was conducted by under the direction of Samples were analyzed under the direction of , Ph.D. The starting date was June 19, 1996. Samples were analyzed from June to August 8, 1996. The total sample storage time was approximately 60 days.

SCREENING FOR STUDY ENTRY

Within 3 weeks prior to the first treatment subjects had to undergo a pre-study check, to evaluate their eligibility with regard to inclusion and exclusion criteria. The pre-study check included assessment of demographic data, medical history, previous and current medication, a physical examination, measurement of vital signs (sitting systolic and diastolic blood pressure and heart rate) and a 12-lead ECG in the supine position.

The following laboratory tests were performed:

Haematology:	Hb, RBC, WBC and differential counts, platelets, hematocrit.
Blood chemistry:	Creatinine, urea, uric acid, total protein, glucose, total bilirubin, SOOT, SGPT, γ-GT, sodium, potassium.
Urinalysis:	by dipsticks: Protein, glucose, RBC, pH
Virology:	HIV (core antibodies) and hepatitis B and C (antibodies and antigen)

Preanancy test: Biosign^{R} hCG one-step method in urine (females only)

Drug screen: Opiates, cannabis, amphetamines.

Characterization of Study Group:

Inclusion criteria

- Subject is male or female between the ages of 18 and 45 years (inclusive)

- Subject has a body weight within 15 % of ideal weight according to Metropolitan Height and Weight Tables, Statistical Bulletin, January-June 1983.

- Subject understands the study procedure and is willing to participate and to give written informed consent.

- Females of childbearing potential (i.e., not status post hysterectomy or tubal ligation) agree to undergo a pregnancy test and to use an appropriate method of contraception (i.e., barrier method or IUD, oral contraceptive steroids) for 1 week before the first treatment until the end of the study.

- Subject is judged to be in good health on the basis of his history and physical examination.

Exclusion Criteria

- Clinically relevant deviation from normal in the routine laboratory tests, in particular serum creatinine > 140 μmol/l, or SGOT, SGPT > 30 % above the upper limit of the normal range.

- Clinically relevant deviation from normal in vital signs and ECG.

- Subject underwent surgery of the gastro-intestinal tract, except appendectomy, that may affect the pharmacokinetic outcome of the study.

- Subject is mentally or legally incapacitated, or has a history of significant psychiatric disorder.

- Subject has donated a unit of blood, or participated in another clinical trial with drugs showing half-lives > 7 days, within the last 4 weeks before the first treatment.

- Subject has a history of any illness that, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering diclofenac to the subject.

- Subject has a history of drug or alcohol abuse and/or shows a positive drug screen.

- Subject has an excessive intake on a habitual basis of more than two- drinks of alcoholic beverages (beer, wine, or distilled spirits) per day.

- Subject is smoking more than 10 cigarettes per day.

- Subject has used any prescription medication within 14 days, or any nonprescription medication within 7 days, before the first treatment, except for oral contraceptive steroids.

- Subject is allergic to diclofenac and/or other NSAIDs.

- Subject is HIV-seropositive or Hepatitis B or C surface antigen positive.

- Subject is pregnant and/or nursing mother.

Concomitant Medication and Treatment

During the course of the study no other medications were allowed, except medication for the treatment of adverse events. If treatment became necessary, the medication(s) was reported on the appropriate section of the Case Report Forms, including generic name, indication, total daily dose, route and time/duration of administration.

Hospitalization

Subjects reported to the clinical unit at about 10 p.m. in the evening prior to a day of treatment, and they remained hospitalized until 12 hours after drug intake.

Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

Study Conduct

The study was done in 48 healthy individuals (20 females; 28 males).
Subjects fasted overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

The products employed in the study were:

Test: /Martec Pharmaceutical 75mg diclofenac enteric-coated tablet, Lot # 960105, potency 102.97%.

Reference: Geigy 75mg Voltaren enteric- coated tablet, Lot # LT4961, potency 100.10%, expiration date not given.

There was a 2 to 3 week washout between doses.

A 75 mg dose (1 x 75 mg) of each product (test and reference) was administered at time zero with .nl of water. The randomization scheme is presented in Table 1.

Table 1. Random Assignment of 48 subjects

Sequence	SUBJECT
A,B	2,3,6,7,8,9,13,16,18,20,22,24,26,29,30,32,33,35,37,38,42,43,46,47
B,A	1,4,5,10,11,12,14,15,17,19,21,23,25,27,28,31,34,36,39,40,41,44,45

Treatment A: Diclofenac tablets, 75 mg (1 Tablet) Ratiopharm GmbH/Martec Pharmaceutical Inc.

Treatment B: Voltaren Tablet, 75 mg (1 Tablet) Geigy

The formulation for the 75 mg tablet is given in table 2.

Table 2. COMPOSITION OF THE 75 MG Diclofenac TABLET-See Appended table.

Plasma was collected -30 to -5 min pre-dose and at the following times

post-dose: 0.5, 1, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.25, 4, 4.5, 5, 5.5, 6, 7, 8, 10 and 12 hours.

During the study subjects were monitored for adverse reactions.

RESULTS

Analytical

The assay procedure, with ι was specific for diclofenac with no interfering chromatographic peaks. Sample and control concentrations were determined by interpolation of their peak areas from the standard curve obtained in the same run. The assay did not use an internal standard.

Assay sensitivity:

The assay was linear over the range c -2000 ng/ml. The limit of sensitivity of the assay was defined as l with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The coefficient of variation was 7.3% at a concentration of 60 ng/ml and 6.0% at 1600 ng/ml. Accuracy of the assay was 93.2% at 60 ng/ml and 99.1 % at 1600 ng/ml.

Absolute recovery of diclofenac measured on was :

Conc.	% Recovery	%CV
15.0 ng/ml	96.3	2.3
400.0 ng/ml	84.7	2.0
800.0 ng/ml	86.0	0.8

Stability

Long Term Stability

Nine QC1 and QC3 samples were stored at -25°C from March 28, 1996, during one month and at -70°C or lower for two more months. After one, two and three months(May 3, June 4, July 4, 1996) they were thawed and analyzed together with freshly spiked QC1 and QC3 samples. Values are mean peak areas (±cv)

	Stability Samples	Comparison Samples
	1 Month	
60 ng/ml	1632(5.81)	1572(4.16)
800 ng/ml	28700(2.07)	26424(1.56)
	2 Months	
60 ng/ml	2355(9.47)	2416(3.45)
800 ng/ml	34456(1.08)	33896(0.34)
	3 Months	

60 ng/ml	1731(2.44)	1553(3.01)
800 ng/ml	28984(2.09)	25969(0.66)

Freeze Thaw

Three QC1 And QC3 samples were subjected to three freeze thaw cycles. After the last thawing they were analyzed and their peak areas compared against peak areas of the corresponding QC samples from the recovery experiment.

	Stability Samples Mean Pk Area	Per Cent Decrease
60 ng/ml	2063	7.4%
800 ng/ml	29049	2.5%

Short Term Stability

Three QC1 and three QC3 samples (preparation March 27, 1996) were thawed on May 3, 1996, and left on the bench. After 4 hr they were worked up together with three QC1 and QC3 samples and stored in the refrigerator for the same time.

	Stability Samples Mean Pk Area	Per Cent Change
60 ng/ml-room	1756	1.01%
60 ng/ml-refr	1732	
800 ng/ml-room	29438	1.01%
800 ng/ml-refr	29069	

There was no effect on stability from storing samples on the bench for 4 hrs.

Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.
Log-transformed data was submitted for analysis.

RESULTS

Table 3.Diclofenac mean plasma levels, ng/ml (±sd), for the subjects that received the 75 mg test and reference formulations after an overnight fast. Values are based upon calculations done by the reviewer(N=47). Values for subject #13 were excluded since the firm reported this subject to have an interfering peak in period 2. Concentrations calculated by the firm are in Appendix A.

Sample Time, HR	Test-Martec	Reference-Voltaren
0.0	0.00(0.00)	0.00(0.00)
0.50	44.69(186.33)	208.85(778.61)
1.00	410.31(730.28)	486.79(795.90)
1.50	1115.78(1126.41)	788.45(989.21)
2.00	863.40(653.02)	826.41(755.82)
2.25	756.46(666.69)	747.03(624.67)
2.50	653.58(604.05)	698.99(575.60)
2.75	416.51(426.62)	503.65(466.05)
3.00	352.39(584.48)	383.26(355.36)
3.25	262.12(413.97)	340.94(436.56)
3.50	216.57(514.87)	271.72(387.84)
4.00	104.11(130.32)	148.21(184.26)
4.50	97.45(222.67)	91.72(78.16)
5.00	54.93(86.82)	54.11(43.72)
5.50	27.28(34.75)	31.18(24.82)
6.00	16.30(18.93)	16.36(19.56)
7.00	3.65(10.01)	4.71(9.95)
8.00	0.75(5.21)	1.05(5.08)
10.00	0.92(6.34)	0.00
12.00	1.28(8.79)	0.00

Table 4.Summary of Mean Bioavailability Parameters for Diclofenac 75 mg dose for Arithmetic Means. Values are mean± SD. All values based upon reviewers calculations (N=47). Values for subject #13 were excluded since the firm reported this subject to have an interfering peak in period 2. Parameters given by the firm are in Appendix B.

	Test		Reference	
Variable	Mean	Std Dev	Mean	Std Dev
AUCL[1] ng/ml x hr	1962.70	488.12	2003.49	583.43
AUCI[2] ng/ml x hr	2028.35	487.68	2042.13	607.42
CMAX ng/ml	2068.06	799.56	2003.04	693.04
TMAX hr	1.9	0.70	1.8	0.7
KELM hr-1	0.94	0.26	1.01	0.25
THALF hr	0.79	0.24	0.73	0.19

1.AUC to the last measurable plasma concentration
2.AUC to infinity

Table 5.Summary of Mean Bioavailability Parameters for 75 mg Diclofenac Based on Least Square Means as Calculated by the reviewer (N=47 except for Cmax).

Test		Reference	Ratio T/R
Variable	Mean	Mean	
LAUCL[1] ng/ml x hr	7.554 (1908.36)[3]	7.565 (1929.47)	98.9[4]
LAUCI[2] ng/ml x hr	7.565 (1929.46)	7.578 (1954.71)	98.7
LCMAX ng/ml	7.546 (1893.15)	7.534 (1888.24)	100.2
LCMAX[5] ng/ml	7.504 (1815.29)	7.509 (1824.39)	99.5

1.AUC to the last measurable plasma concentration
2.AUC to infinity
3.(Geometric Mean)
4 Ratio of Geometric Means x 100
5ubjects deleted that had first concentration as the observed
Cmax(1,4,5,8,11,13,14,16,17,19,20,21,22,23,24,31,32,35,36,40-44,46,48),N=21

Table 6. 90% Confidence Intervals

Parameter	
UCL	(93.7-104.3)
LAUCI	(93.2-104.7)
LCmax	(92.6-110.4)
LCmax*	(89.2-110.9)

*Deleted subjects values that had first observed concentration as Cmax.

Data Comparison Firm vs Reviewer

The mean plasma concentration values were the same as those estimated by the firm however, the parameter values were slightly different. Nonetheless the CI resulting from the analysis by the reviewer and the firm indicated that the study met the CI criterion.

Subject Drop-outs

All 48 subjects completed the study but the data for subject 13 was excluded from pharmacokinetic analysis due to interference in the ;

Sample Repeats

e presentation of the repeat sample analysis data made it difficult to interpret. However, it appears from Table 5.2 page 19/32 volume 3.5 that subject 1 had a repeat analysis done on his data.

Adverse Events

A total of 5 non-serious adverse events were reported by 5 subjects. Mild headache judged to be remotely related to test medication was reported once. Moderate headache, remotely or possibly related was reported three times. The detailed information is given in appended Table 7.

50 MG FASTING STUDY

~BJECTIVES

The purpose of the study is to investigate whether the new delayed release formulation of diclofenac-Na 50 mg 'Martec Pharmaceutical, Inc.) is bioequivalent under fasting conditions to the reference formulation Voltaren 50 mg biconvex, triangular-shaped enteric-coated tablets(Ciba-Geigy).

Methods:

The study was conducted by
B under the direction of). Samples were analyzed under the direction of). The period of the trial was February 1996-March 1996. Samples were analyzed from March 27 to June 13, 1996. The total sample storage time was approximately 120 days.

Inclusion and exclusion criteria were the same as for the 75 mg fasted study.

Study Conduct

The study was done in 48 healthy subjects (25 females; 23 males).
bjects fasted overnight until 4.0 hrs after their scheduled dosing times. Water was not owed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

The products employed in the study were:

Test: 'Martec Pharmaceutical 50 mg diclofenac enteric-coated tablet, Lot # 960103, potency 99.05%.

Reference:Geigy 50mg Voltaren enteric- coated tablet, Lot # LT4101,potency 101.36%, expiration date not given.

There was a 2 to 3 week washout between doses.

A 50 mg dose (1 x 50 mg) of each product (test and reference) was administered at time zero with water. The randomization scheme is presented in Table 8.

Table 8. Random Assignment of 48 subjects

Sequence	SUBJECT
A,B	1,4,6,10,11,12,15,17,18,20,22,24,26,27,28,31,34,36,38,40,41,44,45, 47
B,A	2,3,5,7,8,913,14,16,19,21,23,25,29,30,32,33,35,37,39,42,43,46,48

Treatment A: Diclofenac tablets, 50 mg (1 Tablet) Martec Pharmaceutical Inc.

Treatment B: Voltaren Tablet, 50 mg (1 Tablet) Geigy

The formulation for the 50 mg tablet is given in appended Table C.

Plasma was collected -30 to -5 min pre-dose and at the following times post-dose: 0.5, 1, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.25, 4, 4.5, 5, 5.5, 6, 7, 8, 10 and 12 hours.

During the study subjects were monitored for adverse reactions.

alytical

The assay procedure was specific for diclofenac with no interfering chromatographic peaks. Sample and control concentrations were determined by interpolation of their peak areas from the standard curve obtained in the same run. The assay did not use an internal standard.

Assay sensitivity:

The assay was linear over the range of 20-1250 ng/ml. The limit of sensitivity of the assay was defined as 20 ng/ml with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The coefficient of variation was 7.0% at a concentration of 60 ng/ml and 3.3% at 800 ng/ml. Accuracy of the assay was 94% at 60 ng/ml and 97.2 % at 800 ng/ml.

Pre-assay validation and recovery data was presented for the 75 mg fasting study.

Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

RESULTS

Table 9. Diclofenac mean plasma levels, ng/ml (±sd), for the subjects that received the 50 mg test and reference formulations after an overnight fast. Values are based upon calculations done by the reviewer (N=47). Concentrations calculated by the firm are in Appendix D.

Sample Time,Hrs	Test-Martec	Reference-Voltaren
0.0	0.00(0.00)	0.60(4.11)
0.50	1.34(9.22)	119.28(476.23)
1.00	209.25(483.58)	315.98(567.50)
1.50	570.83(675.47)	448.78(529.32)
2.00	536.17(610.52)	451.37(425.95)
2.25	385.62(439.58)	408.26(452.69)
2.50	313.65(415.14)	345.38(307.42)
2.75	235.24(290.00)	334.26(466.10)
3.00	199.67(356.57)	234.03(302.21)
3.25	161.73(254.24)	155.13(163.21)
3.50	129.04(216.10)	110.73(88.39)
4.00	109.14(288.57)	74.43(73.04)
4.50	66.02(133.83)	52.44(57.81)
5.00	34.46(56.60)	26.57(26.58)
5.50	24.75(36.80)	15.69(18.09)
6.00	11.63(30.78)	9.90(15.33)
7.00	2.92(9.90)	1.71(6.80)
8.00	1.02(4.97)	0.44(3.00)
10.00	0.22(1.53)	0
12.00	0	0

Table 10 .Summary of Mean Bioavailability Parameters for Diclofenac 50 mg dose for Arithmetic Means. Values are mean ± SD. All values are based upon reviewers calculations (N=47). Parameters given by the firm are in Appendix E.

	Test		Reference	
Variable	Mean	Std Dev	Mean	Std Dev
AUCL[1] ng/ml x hr	1094.95	401.05	1116.60	403.43
AUCI[2] ng/ml x hr	1164.14	412.53	1218.76	408.54
CMAX ng/ml	1297.53	637.96	1202.96	560.74
TMAX hr	1.9	0.80	1.8	0.7
KELM hr-1	0.73	0.23	0.88	0.45
THALF hr	1.05	0.36	1.01	0.55

1.AUC to the last measurable plasma concentration
2.AUC to infinity

Table 11.Summary of Mean Bioavailability Parameters for 50 mg Diclofenac Based on Least Square Means as Calculated by the reviewer (N=47 except for Cmax).

Test		Reference	Ratio T/R
Variable	Mean	Mean	
LAUCL[1] ng/ml x hr	6.930 (1022.49)[3]	6.955 (1048.38)	97.5[4]
LAUCI[2] ng/ml x hr	6.996 (1092.25)	7.028 (1127.77)	96.8
LCMAX ng/ml	7.0399 (1141.27)	6.9769 (1071.59)	106.5
LCMAX[5] ng/ml	6.913 (1005.26)	6.902 (994.26)	101.10

1.AUC to the last measurable plasma concentration
2.AUC to infinity
3.(Geometric Mean)
4.Ratio of Geometric Means x 100
5 Subjects deleted that had first concentration as the observed max(1,2,3,4,5,6,8,9,11,12,13,16,17,18,20,21,22,23,24,25,26,27,29, 30,33,35,36,37,38,40,41,43,44,46), N=13

Table 12 . 90% Confidence Intervals

Parameter	
LAUCL	(87.9-108.1)
LAUCI	(86.3-108.6)
LCMAX	(91.2-124.3)
LCMAX*	(67.8-150.7)

*Deleted subjects values that had first observed concentration as Cmax.

Data Comparison Firm vs Reviewer

The mean plasma concentration values were the same as those estimated by the firm however, the parameter values were slightly different since it appeared that the firm included the data for subject 32 whom was "prematurely withdrawn from the study" in their analysis but the data for this subject was not included on their data diskette.

Subject Drop-outs

Only 47 subjects completed the study due to the occurrence of a syncope (fainting) prior to drug administration in period 2 for subject 32.

Sample Repeats

The presentation of the repeat sample analysis data made it difficult to interpret. However, it appears from Table 5.2 page 19/30, attachment 1, volume 3.1 that subjects 1, 15,16 17, 27-29 had a repeat analysis done on their data.

Adverse Events

A total of 4 non-serious adverse events were reported by 4 subjects. Mild dizziness, reported twice, was judged to be possibly related to dicclofenac administration. Moderate headache was judged to be remotely related, whereas syncope, occurring prior to drug administration was judged to be unrelated. The detailed information is given in appended Table 13.

FOOD EFFECT STUDY

ıjective

The purpose of the study was to investigate the possible effect of food (standard breakfast) on the pharmacokinetics of a new delayed-release formulation of diclofenac-Na 75 mg . - ſartec Pharmaceutical, Inc.), and to assess bioequivalence under fed conditions, as compared to the commercial tablet Voltaren[R] 75 mg (Ciba-Geigy).

METHODS

Study Design

This was a single center, open-label, randomized, 3-period cross-over study, in which 21 healthy male and female subjects received a single dose of 75 mg diclofenac on 3 occasions with an interval between 2 and 3 weeks. One dose was administered as the new formulation (test formulation) with subjects in the fasted or fed state and the other dose as the commercial formulation Voltaren° (Ciba-Geigy; reference) with subjects in the fed state.

The study was conducted by : . Samples were analyzed under ·'e direction of The study was conducted between April and May 1996. mples were analyzed from July 12, 1996 to July 29, 1996. The total sample storage time was approximately 120 days.

Inclusion and exclusion criteria were the same as for the 75 mg fasted study.

Study Conduct

The study was done in 21 healthy male and female subjects (10 males ;11 females).

Subjects fasted overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

The products employed in the study were:

Test: F 'Martec Pharmaceutical 75 mg diclofenac enteric-coated tablet, Lot # 960105, potency 102.97%.

Reference:Geigy 75mg Voltaren enteric- coated tablet, Lot # LT4961,potency 100.10%, expiration date not given.

There was a 2 to 3 week washout between doses.

• 75 mg dose (1 x 75 mg) of each product (test and reference) was administered at time zero with of water. The randomization scheme is presented in Table 14.

Table 14. Random Assignment of 21 subjects

Sequence	SUBJECT
A,B,C	8,9,11,19
B,C,A	1,4,7,10
C,A,B	2,5,6,13
A,C,B	3,15,21
C,B,A	12,14,18
B,A,C	16,17,20

Treatment A: Diclofenac tablets, 75 mg (1 Tablet) H/Martec Pharmaceutical Inc.
Fasted
eatment B: Diclofenac tablets, 75 mg (1 Tablet) Martec Pharmaceutical Inc.
Fed
Treatment C: Voltaren Tablet, 75 mg (1 Tablet) Geigy
Fed

Plasma was collected -30 to -5 min pre-dose and at the following times post-dose: 0.5, 1, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.25, 4, 4.5, 5, 5.5, 6, 7, 8, 10 and 12 hours.

There were no special dietary requirements. Subjects who received treatment in the fasted state (treatment A) had fasted overnight for 10 hours and remained fasting until lunch, at 4 hours after drug administration.

Subjects who received treatments in the fed state (treatments B and C) were served a standardized breakfast. Subjects started consuming the breakfast 20 minutes before drug administration. They were requested to finish the breakfast completely within 15 minutes. Within 5 minutes after finishing breakfast one tablet of diclofenac was administered. The standardized breakfast consisted of:

Two fried eggs
ıe slice of toast with a pat of butter (10 g) and jelly (20 g)
ıwo strips of bacon
4 ounces (= 113 g) of hash brown potatoes

8 ounces (= 227 ml) of whole milk.

For each subject the medical supervisor or his assistant checked whether the breakfast was consumed completely during the 15 minutes.

A standardized lunch and dinner were consumed at 4 and 10 hours, respectively, after drug administration. The meals consisted of:

Standard lunch	Standard dinner
1 sandwich with low fat cheese	1 pizza
1 sandwich with dry meat	salad
1 apple	200 ml of mineral water or light tea
200 ml of mineral water	

From the time of presentation to the clinical unit, in the evening prior to a day of treatment, until 12 hours after drug administration, smoking, the use of alcohol or methylxanthine containing beverages, as well as grapefruit or orange juice were not allowed. On the days of treatment no fluid was taken from the time of drug administration until 2 hours thereafter, intake of 200 ml of tap water was allowed between 2 hours after drug administration until lunch time, whereas during and after lunch fluid intake was ad libitum.

During the study subjects were monitored for adverse reactions.

Analytical

The assay procedure was specific for diclofenac with no interfering chromatographic peaks. Sample and control concentrations were determined by interpolation of their peak areas from the standard curve obtained in the same run. The assay did not use an internal standard.

Assay sensitivity:

The assay was linear over the range of 20-2000 ng/ml. The limit of sensitivity of the assay was defined as 20 ng/ml with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The coefficient of variation was 9.8% at a concentration of 50 ng/ml and 6.3% at 1600 ng/ml. Accuracy of the assay was 99% at 50 ng/ml and 100 % at 1600 ng/ml.

Pre-assay validation and recovery data was presented for the 75 mg fasting study.

Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

Results

ole 15 . Diclofenac mean plasma levels, ng/ml (±sd), for the subjects that received the 75 mg test and reference formulations after a high fat meal or the test following an overnight fast. Values are based upon calculations done by the reviewer(N=21fasted, N=15[1] test fed, N=16[2] reference fed). Concentrations calculated by the firm are in Appendix F.

Sample Time	Diclofenac Fed		Voltaren Fed		Diclofenac Fasting	
Hrs	Mean	± SD	Mean	± SD	Mean	± SD
0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.5	0.0	0.0	0.0	0.0	23.8	109.1
1.0	0.0	0.0	0.0	0.0	245.3	555.3
1.5	0.0	0.0	0.0	0.0	671.9	833.2
2.0	40.3	184.6	0.0	0.0	918.3	693.7
2.5	56.8	260.3	0.0	0.0	498.2	421.4
3.0	25.3	115.9	0.0	0.0	381.0	592.1
.5	273.4	1052.7	7.9	36.0	141.2	197.1
4.0	196.5	551.5	155.9	442.3	86.6	86.5
4.5	482.3	792.0	631.1	1006.9	128.2	342.9
5.0	588.3	802.8	498.7	587.7	44.9	46.5
5.5	326.5	510.0	459.8	576.4	22.6	24.7
6.0	156.3	248.7	163.9	235.9	11.8	16.4
6.5	64.7	91.0	68.2	79.5	2.3	7.1
7.0	38.4	47.8	43.8	64.9	2.1	6.7
8.0	68.4	244.9	14.2	17.0	0	0.0
10.0	60.0	270.2	2.4	10.9	0	0.0
12.0	8.9	41.0	59.0	149. 6	0	0.0

[1]Subjects 9, 10, 12, 16, 20, 21 had no measurable plasma concentrations
[2]ubjects 9, 11, 14, 18, 20 had no measurable plasma concentrations

Table 16. Summary of Arithmetic Mean Bioavailability Parameters for Diclofenac 75 mg tablet dose under fasting and post-prandial conditions. Values are mean ± SD. All values are based upon reviewers calculations(N values are the same as for Table 15). Parameters given by the firm are in Appendices G, H and I.

TREATMENT				
Variable	Test-Fed	Reference-Fed	Test-Fasted	Ratio x 100 T/R Fed
AUCL[1](ng hr/ml)	1264.32± 417.06	1044.94± 500.58	1159.92± 488.86	121
AUCI[2](ng hr/ml)	1315.35± 445.87	1178.62± 428.44	1290.91± 587.47	112
Cmax (ng/ml)	1765.60± 1031.72	1408.44± 837.74	1607.38± 648.72	125
KEL-1 (hr)	1.19±0.33	1.46±0.38	0.98±0.3	
HALF (hr)	0.64	0.51	0.78	
TPEAK (hr)	5.2	6.3	2.1	

[1]AUCL = AUC (0 to last measurable concentration)
UCI = AUC (0 - infinity)

Table 17. Summary of Mean Bioavailability Parameters for the post-prandial 75 mg Diclofenac study Based on Least Square Means as Calculated by the reviewer(N is the same as for Table except for Cmax).

Test - Fed		Reference Fed	Test - Fasting	Ratio x 100 T/R Fed
Variable	Mean	Mean		
LAUCL[1] ng/ml x hr	7.07 (1179.80)[3]	6.91 (1010.36)	6.97	110.5[4]
LAUCI[2] ng/ml x hr	6.94 (1030.11)	7.06 (1160.63)	6.87	110.5
LCMAX ng/ml	7.347 (1551.5)	7.211 (1354.2)	7.308	114.6
LCMAX[5] ng/ml	7.412 (1655.57)	7.719 (2251.25)	7.313	73.5

1. AUC to the last measurable plasma concentration
2. AUC to infinity

3.(Geometric Mean)
4.Ratio of Geometric Means x 100
5 Subjects deleted that had the first concentration as the observed Cmax or less than concentrations, (Test-Fasting 10, 16, 18, 21); (Test-Fed 2, 7, 14,15, 18); (Reference-Fed 2, 5, 7, 12, 15, 16, 17, 19, 21)

Data Comparison Firm vs Reviewer

The mean plasma concentration values were the same as those estimated by the firm however, the parameter values were different since the firm used 3 procedures to analyze their data. These procedures were :
Method I- Estimating parameters for subjects including those with less than 2 plasma concentrations above the limit of quantitation.
Method II- Estimating parameters for subjects and excluding those with less than 3 plasma concentrations above the limit of quantitation.
Method III- Estimating parameters for subjects evaluable by methods I and II.

The reviewers procedure was to delete the subjects whose treatments resulted in less than 4 plasma concentrations.

Subject Drop-outs

There were no subject drop-outs.

mple Repeats

The presentation of the repeat sample analysis data made it difficult to interpret. However, it appears from Table 5.2 page 18/24, in attachment 1, volume 3.6 that subjects 21 and 10 had a repeat analysis done on their data.

Adverse Events

There was one adverse event (moderate headache) reported by a subject after taking the test product in the fed state. The detailed information on adverse events given in appended Table 18.

Dissolution

The dissolution study for diclofenac was done as follows:

Apparatus:	Paddle, 50 RPM
Medium:	900 ml 0.1 N HCL (2 hours) Medium changed to: 1000 ml pH 6.8 buffer
No. of Units Analyzed:	12
ecifications:	

Assay:

This is not an official USP method since USP 23 supplement #6 (May 15, 1997) uses 900 ml of buffer. The results are presented in Table 19.

)mments-

1. The 90 % confidence intervals for LnAUC(0-t) and LnAUC(0-inf) and LnCmax for the 75 mg fasting study were acceptable.

2. The 90 % confidence interval for LnCmax following deletion of the subjects that had the first time point as their Cmax for the 50 mg fasting study was unacceptable.

3. The ratio of the geometric means for LnCmax following deletion of the subjects that had the first time point as their Cmax for the 75 mg food study was outside of the acceptable range of 80%-125%.

4. The 50 mg and 75 mg tablets are compositionally proportional for all components except Avicel. The difference in the Avicel is not believed to be important since the dissolution for both strengths was similar.

Overall Deficiencies

1. Starting clinical and analytical dates were not clearly stated by the firm for the 75 mg fasting, 50 mg fasting and 75 mg post-prandial studies.

2. Expiration dates for the reference formulation Lot numbers LT4961 and LT4101 were not presented. Also the lot sizes for 960105 and 960103 for the test drug were not presented.

3. The overall organization of the ANDA was poor and difficult to follow. Finding required study information was difficult and time consuming. In the future the firm should organize the submission by having everything related to a particular dosage strength within the same volume. Also label the tabs according to the contents of that section instead of using designations such as modules and attachments. This organizational structure is very confusing.

4. The protocols for the 75 mg fasting, 50 mg fasting and 75 mg post-prandial studies used smokers. However, it was not clear if they were allowed to smoke during the study. The firm needs to clarify this point.

5. The firm should explain the rationale for preparing calibration samples by merely adding together the required volumes as presented in their protocol instead of preparing them volumetrically (ie.,using volumetric containers).

6. The firm did not supply summary statistics for each calibration curve and information on the amount added and found so that assay precision could not be evaluated.

7. The firm should explain why Table 2 page A7/A20 in volume 3.5 presented under CPR 96-802 the

75 mg study has the table legend for 96-801 which is the 50 mg study?

8. The firm should explain why is there such a big difference in recovery between and in their validation studies.

9. The firm should explain why they did not prepare fresh standards for the freeze/thaw study as they did for the long term stability studies.

10. The firm should explain why the 2 month long term stability data is almost 20% larger (absolute values) at 800 ng/ml and 30% larger for 60 ng/ml compared to the 1 month and 3 month samples.

11. The firm should explain why at 3 months for the long term stability study there is a 10% increase in both concentrations.

12. The firm should explain why they presented data for only 3 months stability when some samples were stored as long as 120 days?

13. The firm did not give the type or normality of the buffer used in the dissolution study.

14. The firm did not describe the assay used in the dissolution study. Also the firm should use 900 ml of pH 6.8 buffer for their dissolution studies instead of 1000ml to be consistent with the USP supplement #6.

15. When the subjects in the 50 mg fasting study that had Cmax as their first measurable time point were excluded from the analysis of the data, the 90% confidence interval for Ln Cmax was 67.8-150.7% which is outside of the acceptable limits of 80-125% of the reference.

16. Deletion of subjects in the 75 mg food study that had Cmax as their first measurable time point resulted in ratios of geometric means for LnCmax of 73.5% which is outside the acceptable limits of 80%-125%.

17. The firm should explain why they included the data for subject #32 in the analysis of their 50 mg study but it was not included on the data diskette submitted to the Division of Bioequivalence. Also why this subject's data analyzed since he exhibited an adverse effect? The firm should also explain what "prematurely withdrawn from the study due to an adverse event" means with respect to subject 32.

18. The firm should not have deleted subjects that have complete plasma profiles for the post-prandial (i.e., Method III) study since the analysis of the data by LSMEANS accounts for the unbalanced study design and calculates appropriately weighted mean paramater value.

Recommendation:

1. The fasting bioequivalence study conducted by Martec on its 75 mg diclofenac tablet, Lot No. 960105, comparing it to Ciba Geigy's Voltaren 75 mg tablet Lot No. LT4961 has been found to be acceptable by the Division of Bioequivalence. The bioequivalence studies conducted by Martec on its 50 mg diclofenac tablet, Lot No. 960103 and the food study on the 75 mg diclofenac tablet, Lot No. 960105, comparing them to Ciba Geigy's Voltaren 50 mg tablet Lot No. LT401 and Voltaren 75 mg tablet Lot No. LT4961 respectively, have been found to be unacceptable by the Division of Bioequivalence. Therefore, the overall application is found to be unacceptable to the Division of Bioequivalence.

2. The dissolution testing conducted by Martec on the 75 mg strength, Lot No. 960105 and the 50 mg strength Lot No. 960103 has been found to be incomplete.

3. The firm should receive comments 1-4 and deficiencies 1-18.

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

/S/

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ Date: 9/30/97

ncur: /S/ Date: 10/5/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalenc

ckson), Drug

Table 19 . In Vitro Dissolution Testing

Drug (Generic Name):Diclofenac
Dose Strength:75 mg and 50 mg
ANDA No.:74-986
Firm:Martec
Submission Date:June 10, 1997
File Name:74986SD.697

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 50
No. Units Tested: 12
Medium: 0.1 N HCL
PH 6.8 buffer
Volume:900 ml
1000 ml
Specifications:

Reference Drug: Voltaren
Assay Methodology:

Results of In Vitro Dissolution Testing: Acid

Sampling Times (Minutes)	Test Product Lot # 960103 Strength(mg) 50			Reference Product Lot # LT4101 Strength(mg) 50		
	Mean %	Range	%CV	Mean %	Range	%CV
30	0.23		25.25	0.37		19.21
60	0.19		34.57	0.23		38.34
120	0.35		22.95	0.57		22.17

Sampling Times (Minutes)	Test Product-Buffer Lot # 960103 Strength(mg) 50			Reference Product Lot # LT4101 Strength(mg) 50		
	Mean	Range	%CV	Mean	Range	%CV
5	3.63		262	0.78		4.1
10	69.31		38	32.73		2.9
20	91.11		7.04	79.65		1.7
30	93.43		4.52	84.69		1.2
5	94.61		4.07	88.39		1.4

Sampling Times Minutes	Test Product-Acid Lot # 960105 Strength(mg) 75			Reference Product Lot # LT4961 Strength(mg) 75		
	Mean	Range	%CV	Mean	Range	%CV
30	0.24		36	0.12		22
60	0.12		29	0.11		32
120	0.31		25	0.20		29

Sampling Times Minutes	Test Product-Buffer Lot # 960105 Strength(mg) 75			Reference Product Lot # LT4961 Strength(mg) 75		
	Mean	Range	%CV	Mean	Range	%CV
5	1.69		3.2	0.42		315.15
10	44.34		35.29	7.82		123.82
20	92.29		15.95	79.27		7.92
0	93.48		7.03	90.31		1.66
45	94.89		6.06	92.57		1.37

4.1

ANDA 74-986

OCT 17 1997

Martec Pharmaceutical, Inc.
Attention: Paul T. Sudhakar
1800 N. Topping
P. O. Box 33510
Kansas City, MO 64120

Dear Sir:

Reference is made to the Abbreviated New Drug Application and the amendments submitted on June 10 and 26, 1997, for Diclofenac Sodium Delayed-Release Tablets, 75 mg and 50 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The experience of this division is that data from those subjects whose Cmax is attained at the first sampling point is generally undependable.

   a. The 90 % confidence interval for LnCmax following deletion of the subjects that had the first time point as their Cmax for the 50 mg fasting study was unacceptable.

   b. The ratio of the geometric means for LnCmax following deletion of the subjects that had the first time point as their Cmax for the 75 mg food study was outside of the acceptable range of 80%-125%.

2. We have no further questions on the fasting bioequivalence study on the 75 mg diclofenac tablet.

3. The bioequivalence studies conducted on the 50 mg diclofenac tablet and the food study on the 75 mg diclofenac tablet have been found unacceptable by the Division of Bioequivalence for these reasons:

   a. Starting clinical and analytical dates were not clearly stated for any of the studies.

   b Expiration dates for the reference formulation Lot numbers LT4961 and LT4101 were not presented. Also the lot sizes for 960105 and 960103 for the test drug were missing.

c. The overall organization of the ANDA was poor and difficult to follow. Finding required study information was difficult and quite time consuming. In the future the firm should organize the submission by having everything related to a particular dosage strength within the same volume. Also label the tabs according to the contents of that section instead of using designations such as modules and attachments. This organizational structure is very confusing.

d. The protocols for the 75 mg fasting, 50 mg fasting and 75 mg post-prandial studies used smokers. However, it was not clear if they were permitted to smoke during the study. Please clarify this point.

e. Explain the rationale for preparing calibration samples by merely adding together the required volumes as presented in their protocol instead of preparing them volumetrically (ie.,using volumetric containers).

f. Supply summary statistics for each calibration curve and information on the amount added and found so that assay precision can be properly evaluated.

g. Explain why Table 2 page A7/A20 in volume 3.5 presented under CPR 96-802 for the 75 mg study, has the table legend for 96-801, which is the 50 mg study?

h. Explain why is there such a big difference in recovery between › in their validation studies.

i. Why were fresh standards for the freeze/thaw study not prepared, as they were for the long term stability studies.

j. Explain why the 2 month long term stability data is almost 20% larger (absolute values) at 800 ng/mL and 30% larger for 60 ng/mL compared to the 1 month and 3 month samples.

k. Why is there a 10% increase in both concentrations at 3 months for the long term stability study.

l. Why is there data for only 3 months stability when some samples were stored as long as 120 days?

m. Give the type or normality of the buffer used in the dissolution study.

n. Describe the assay method used in the dissolution study. To be consistent with USP supplement #6, use 900 mL of pH 6.8 phosphate buffer instead of

o. When the subjects in the 50 mg fasting study that had Cmax as their first measurable time point were excluded from the analysis of the data, the 90% confidence interval for LnCmax was 67.8-150.7% which is outside of the acceptable limits of 80-125% of the reference.

p. Deletion of subjects in the 75 mg food study that had Cmax as their first measurable time point resulted in ratios of geometric means for LnCmax of 73.5% which is outside the acceptable limits of 80%-125%.

q. Explain why the data for subject #32 was included in the analysis of their 50 mg study, but was not included on the data diskette submitted to the Division of Bioequivalence. Also why was this subject's data analyzed since he exhibited an adverse effect? Also explain what "prematurely withdrawn from the study due to an adverse event" means with respect to subject 32.

r. Subjects that have complete plasma profiles for the post-prandial (i.e., Method III) study should not have been deleted, since the analysis of the data by LSMEANS accounts for the unbalanced study design and calculates appropriately weighted mean paramater value.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Table 2.

COMPONENTS AND COMPOSITION (PER TABLET)
DICLOFENAC SODIUM DELAYED RELEASE TABLETS, 50 MG AND 75 MG (ENTERIC-COATED)

	INGREDIENTS	GRADE	50 MG tablet mg	75 MG tablet mg	VENDOR
GRANULATION (FLUID BED)	Dilcofenac Na		50	75	
	Lactose monohydrate				
	(colloidal silicondioxide)				
	(povidone)				
	TOTAL WEIGHT GRANULATION				
EXTERNAL PHASE GRANULATION (BLEND)	Sodium stearylfumarate				
	(crospovidone)				
	(microcrystalline cellulose)				
	TOTAL WEIGHT EXTERNAL PHASE				
	TOTAL WEIGHT CORE				
ENTE COATING	talc				
	(methacrylic acid copolymer)				
	Propylene glycol				
	f				
	TOTAL WEIGHT (ENTERIC COAT)				
FINAL COATING	Polyethylene glycol				
	Titanium dioxide				
	TOTAL WEIGHT (FINAL COAT)		7	<5% 7	
	TOTAL WEIGHT COATED TABLETS		385	385	

982000

S9/20/96

Appendix A

2. MEAN PLASMA CONCENTRATIONS OF DICLOFENAC

Plasma concentrations of diclofenac (ng/ml)
Treatment A: Diclofenac-Na 75 mg, delayed release tablet (Ratiopharm)

Time	Mean	SD	Median
baseline	0.00	0.00	0.00
0.5 h	44.7	186	0.00
1.0 h	410	730	0.00
1.5 h	1116	1126	1020
2.0 h	863	653	622
2.25 h	756	667	595
2.5 h	654	604	392
2.75 h	417	427	277
3.0 h	352	584	194
3.25 h	262	414	150
3.5 h	217	515	112
4.0 h	104	130	69.6
4.5 h	97.5	223	52.1
5.0 h	54.9	86.8	38.3
5.5 h	27.3	34.8	23.8
6.0 h	16.3	18.9	0.00
7.0 h	3.65	10.01	0.00
8.0 h	0.760	5.21	0.00
10.0 h	0.926	6.35	0.00
12.0 h	1.28	8.80	0.00

Plasma concentrations of diclofenac (ng/ml)
Treatment B: Voltaren® 75 mg, delayed release tablet

Time	Mean	SD	Median
baseline	0.00	0.00	0.00
0.5 h	209	779	0.00
1.0 h	487	796	0.00
1.5 h	788	989	511
2.0 h	826	756	528
2.25 h	747	625	626
2.5 h	699	576	485
2.75 h	504	466	329
3.0 h	383	355	235
3.25 h	341	437	185
3.5 h	272	388	136
4.0 h	148	184	88.6
4.5 h	91.7	78.2	75.8
5.0 h	54.1	43.7	48.7
5.5 h	31.2	24.8	29.6
6.0 h	16.4	19.6	0.00
7.0 h	4.71	9.9	0.00
8.0 h	1.06	5.1	0.00
10.0 h	0.00	0.0	0.00
12.0 h	0.00	0.0	0.00

Appendix B

5. MEAN PHARMACOKINETIC PARAMETERS OF DICLOFENAC

Treatment A: Diclofenac-Na 75 mg, delayed release tablet (Ratiopharm)

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)				1830		1931	754		39
t_{max} (h)	1.9	0.7		1.50	36				
$t_{½}$ (h)	0.79	0.24		0.77	30				
K_{el} (1/h)	0.94	0.26		0.90	28				
R ass. with K_{el}				0.962					
n ass. with R				8					
AUC_{0-t} (ng.h/ml)				1915		1915	459		24
$AUC_{0-\infty}$ (ng.h/ml)				1945		1949	458		24
F_{rel}				0.97		0.99	0.21		22
MRT_{0-t} (h)	2.25	0.70		2.07	31				

Treatment B: Voltaren® 75 mg, delayed release tablet

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)				1848		1914	571		30
t_{max} (h)	1.8	0.7		1.50	42				
$t_{½}$ (h)	0.73	0.19		0.70	26				
K_{el} (1/h)	1.01	0.25		0.99	25				
R ass. with K_{el}				0.964					
n ass. with R				10					
AUC_{0-t} (ng.h/ml)				1945		1934	532		27
$AUC_{0-\infty}$ (ng.h/ml)				1973		1963	533		27
MRT_{0-t} (h)	2.25	0.70		2.22	31				

75 mg Fasting

1. LISTING OF ADVERSE EVENTS

75 mg Fasting Study

Table 7

Subject	Specification orig. term	Serious	Date of Onset	Time of Onset	Date ceased	Time ceased	Most severe intensity	Relationship to test drug poss.	Frequency cont.	Action taken for Event other	Outcome res. no seq.
14	headache	No	26/04/96	10:35	26/04/96	15:15	mod.				

	Treatment for Event orig. term		Treatment for Event pref. term	Start of admin.	End of admin.	Drug regimen	Route of admin.	Total daily dose	Unit	Time of admin.
paracetamol	(panadol®)	0.5 g tabl	paracetamol	26/04/96	26/04/96	1 x 1	p.o.	500	mg	11.00h

1. LISTING OF ADVERSE EVENTS

75 mg Food Study

Table 18

Listing of Adverse events

Subject	Specification orig. term	Serious	Date of Onset	Time of Onset	Date ceased	Time ceased	Most severe intensity	Relationship to test drug	Frequency	Action taken for Event	Outcome
1	headache	No	05/03/96	9:30	05/03/96	21:00	mod.	rem.	interm.	other	res. no seq.
2	vagal reaction	No	21/03/96	8:07	21/03/96	10:40	mild	unrel.	interm.	none	res. no seq.
31	headache	No	08/03/96	16:30	08/03/96	19:30	mild	rem.	cont.	none	res. no seq.
32	headache	No	08/03/96	14:10	08/03/96	20:00	mod.	poss.	cont.	none	res. no seq.
35	headache	No	08/03/96	12:45	08/03/96	20:00	mod.	poss.	cont.	other	res. no seq.

Subject	Specification orig. term	Treatment for Event orig. term	Treatment for Event pref. term	Start of admin.	End of admin.	Drug regimen	Route of admin.	Total daily dose	Unit	Time of admin.
1	headache	paracetamol (Panadol®) 0.5 supp	paracetamol	05/03/96	05/03/96	2x1	p.a.	1000	mg	11.15h; 18.20h
2	vagal reaction	.	.	.	.	.	.	.	.	.
31	headache	.	.	.	.	.	.	.	.	.
32	headache	.	.	.	.	.	.	.	.	.
35	headache	paracetamol (Panadol®) 0.5 supp	paracetamol	08/03/96	08/03/96	1x1	p.a.	500	mg	18.30h

9. MEAN PHARMACOKINETIC PARAMETERS OF DICLOFENAC - method 3

Method 3: Only subjects that are evaluable (according to method 2) both in treatment B and C were included for the calculations in treatment B and C

Treatment C: Voltaren® 75 mg, delayed release tablet - FED STATE

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)	1805	787		1690	44	1671	708		42
t_{max} (h)	4.8	0.5		4.5	11				
$t_{½}$ (h)	0.53	0.16		0.51	31				
k_{el} (1/h)	1.42	0.42		1.38	30				
r ass. with k_{el}				0.940					
n ass. with R				5					
AUC_{0-t} (ng.h/ml)	1819	430		1888	24	1769	463		26
$AUC_{0-\infty}$ (ng.h/ml)	1842	427		1903	23	1793	458		26
MRT_{0-t} (h)	5.06	0.50		4.92	10				

Appendix I

9. MEAN PHARMACOKINETIC PARAMETERS OF DICLOFENAC - method 3

Method 3: Only subjects that are evaluable (according to method 2) both in treatment B and C were included for the calculations in treatment B and C

Treatment A: Diclofenac-Na 75 mg, delayed release tablet (Ratiopharm) - FASTED STATE

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)	1607	649		1613	40	1477	684		46
t_{max} (h)	2.1	0.8		2.0	36				
$t_{½}$ (1/h)	0.78	0.25		0.72	32				
k_{el} (1/h)	0.98	0.30		0.96	30				
r ass. with k_{el}				0.935					
n ass. with R				6					
AUC_{0-t} (ng.h/ml)	1582	513		1409	32	1503	511		34
$AUC_{0-\infty}$ (ng.h/ml)	1612	516		1444	32	1534	514		33
MRT_{0-t} (h)	2.37	0.72		2.32	30				

Treatment B: Diclofenac-Na 75 [illegible] tablet (Ratiopharm) - FED STATE

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)	1691	677		1681	40	1569	682		43
t_{max} (h)	4.6	0.8		4.8	18				
$t_{½}$ (1/h)	0.64	0.25		0.59	40				
k_{el} (1/h)	1.20	0.36		1.18	30				
r ass. with k_{el}				0.942					
n ass. with R				6					
AUC_{0-t} (ng.h/ml)	1703	472		1688	28	1642	484		29
$AUC_{0-\infty}$ (ng.h/ml)	1730	476		1707	28	1669	487		29
MRT_{0-t} (h)	4.84	0.89		5.05	18				

7. MEAN PHARMACOKINETIC PARAMETERS OF DICLOFENAC - method 2

Method 2: Subjects with less than 3 plasma measurements above lower limit of quanitification are excluded

Treatment C: Voltaren® 75 mg, delayed release tablet - FED STATE

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)	1640	752		1461	46	1512	636		42
t_{max} (h)	4.9	0.5		5.0	11				
$t_{½}$ (h)	0.51	0.15		0.46	30				
k_{el} (1/h)	1.46	0.38		1.51	26				
r ass. with k_{el}				0.942					
n ass. with R				5					
AUC_{0-t} (ng.h/ml)	1667	475		1781	28	1603	484		30
$AUC_{0-\infty}$ (ng.h/ml)	1689	474		1806	28	1626	483		30
MRT_{0-t} (h)	5.19	0.52		5.24	10				

Appendix H

7. MEAN PHARMACOKINETIC PARAMETERS OF DICLOFENAC - method 2

Method 2: Subjects with less than 3 plasma measurements above lower limit of quantification are excluded

Treatment A: Diclofenac-Na 75 mg, delayed release tablet (Ratiopharm) - FASTED STATE

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower - upper limit	CV (%)
C_{max} (ng/ml)	1607	649		1613	40	1477	684		46
t_{max} (h)	2.1	0.8		2.0	36				
$t_{½}$ (h)	0.78	0.25		0.72	32				
k_{el} (1/h)	0.98	0.30		0.96	30				
r ass. with k_{el}				0.935					
n ass. with R				6					
AUC_{0-t} (ng.h/ml)	1582	513		1409	32	1503	511		34
$AUC_{0-\infty}$ (ng.h/ml)	1612	516		1444	32	1534	514		33
MRT_{0-t} (h)	2.37	0.72		2.32	30				

Treatment B: Diclofenac-Na 75 mg, delayed release tablet (Ratiopharm) - FED STATE

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower - upper limit	CV (%)
C_{max} (ng/ml)	1855	1085		1438	58	1637	872		53
t_{max} (h)	4.6	0.9		5.0	19				
$t_{½}$ (h)	0.63	0.23		0.57	37				
k_{el} (1/h)	1.21	0.34		1.23	28				
r ass. with k_{el}				0.933					
n ass. with R				5					
AUC_{0-t} (ng.h/ml)	1844	801		1868	43	1709	708		41
$AUC_{0-\infty}$ (ng.h/ml)	1873	809		1884	43	1738	712		41
MRT_{0-t} (h)	4.91	0.93		5.11	19				

5. MEAN PHARMACOKINETIC PARAMETERS OF DICLOFENAC - method 1

Method 1: For the calculation of AUC_{0-t} and $AUC_{0-\infty}$ subjects with less than 2 plasma measurements above lower limit of quantification are excluded

Treatment C: Voltaren® 75 mg, delayed release tablet - FED STATE

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)	1073	951		1151	89	1175	870		74
t_{max} (h)	6.3	2.9		5.3	46				
$t_{½}$ (h)	0.51	0.15		0.46	30				
k_{el} (1/h)	1.46	0.38		1.51	26				
r ass. with k_{el}				0.942					
n ass. with R				5					
AUC_{0-t} (ng.h/ml)	1587	547		1650	34	1483	629		42
$AUC_{0-\infty}$ (ng.h/ml)	1689	474		1806	28	1626	483		30
MRT_{0-t} (h)	5.19	0.52		5.24	10				

Appendix G

5. MEAN PHARMACOKINETIC PARAMETERS OF DICLOFENAC - method 1

Method 1: For the calculation of AUC_{0-t} and $AUC_{0-\infty}$ subjects with less than 2 plasma measurements above lower limit of quantification are excluded

Treatment A: Diclofenac-Na 75 mg, delayed release tablet (Ratiopharm).- FASTED STATE

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)	1607	649		1613	40	1477	684		46
t_{max} (h)	2.1	0.8		2.0	36				
$t_{½}$ (h)	0.78	0.25		0.72	32				
k_{el} (1/h)	0.98	0.30		0.96	30				
r ass. with k_{el}				0.935					
n ass. with R				6					
AUC_{0-t} (ng.h/ml)	1582	513		1409	32	1503	511		34
$AUC_{0-\infty}$ (ng.h/ml)	1612	516		1444	32	1534	514		33
MRT_{0-t} (h)	2.37	0.72		2.32	30				

Treatment B: Diclofenac-Na 75 mg, delayed release tablet (Ratiopharm) - FED STATE

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)	1261	1189		1193	94	1568	792		51
t_{max} (h)	5.2	1.8		5.0	34				
$t_{½}$ (h)	0.64	0.23		0.59	35				
k_{el} (1/h)	1.19	0.33		1.18	28				
r ass. with k_{el}				0.942					
n ass. with R				5					
AUC_{0-t} (ng.h/ml)	1903	800		1877	42	1764	736		42
$AUC_{0-\infty}$ (ng.h/ml)	1944	821		1900	42	1801	753		42
MRT_{0-t} (h)	5.28	1.65		5.14	31				

Appendix F

2. MEAN PLASMA CONCENTRATIONS OF DICLOFENAC

Plasma concentrations of diclofenac (ng/ml)
Treatment A: Diclofenac-Na 75 mg, delayed release tablet (Ratiopharm) - FASTED STATE

Period	Mean	SD	Median
baseline	0.00	0.00	0.00
0.5 h	23.8	109	0.00
1.0 h	245	555	0.00
1.5 h	672	833	390
2.0 h	918	694	785
2.5 h	498	421	416
3.0 h	381	592	215
3.5 h	141	198	86.0
4.0 h	86.6	86.5	60.0
4.5 h	128	343	45.3
5.0 h	44.9	46.5	34.9
5.5 h	22.6	24.7	21.8
6.0 h	11.8	16.4	0.00
6.5 h	2.25	7.11	0.00
7.0 h	2.14	6.76	0.00
8.0 h	0.00	0.00	0.00
10.0 h	0.00	0.00	0.00
12.0 h	0.00	0.00	0.00

Plasma concentrations of diclofenac (ng/ml)
Treatment B: Diclofenac-Na75 mg, delayed release tablet (Ratiopharm) - FED STATE

Period	Mean	SD	Median
baseline	0.00	0.00	0.00
0.5 h	0.00	0.00	0.00
1.0 h	0.00	0.00	0.00
1.5 h	0.00	0.00	0.00
2.0 h	40.3	185	0.00
2.5 h	56.8	260	0.00
3.0 h	25.3	116	0.00
3.5 h	273	1053	0.00
4.0 h	196	552	0.00
4.5 h	482	792	0.00
5.0 h	588	803	65.7
5.5 h	327	510	95.9
6.0 h	156	249	50.1
6.5 h	64.7	91.1	48.3
7.0 h	38.4	47.8	22.8
8.0 h	68.4	245	0.00
10.0 h	60.0	270	0.00
12.0 h	8.95	41.0	0.00

Plasma concentrations of diclofenac (ng/ml)
Treatment C: Voltaren® 75 mg, delayed release tablet - FED STATE

Period	Mean	SD	Median
baseline	0.00	0.00	0.00
0.5 h	0.00	0.00	0.00
1.0 h	0.00	0.00	0.00
1.5 h	0.00	0.00	0.00
2.0 h	0.00	0.00	0.00
2.5 h	0.00	0.00	0.00
3.0 h	0.00	0.00	0.00
3.5 h	7.86	36.0	0.00
4.0 h	156	442	0.00
4.5 h	631	1007	0.00
5.0 h	499	588	333
5.5 h	460	576	145
6.0 h	164	236	74.8
6.5 h	68.2	79.5	45.0
7.0 h	43.9	64.9	36.1
8.0 h	14.2	17.0	0.00
10.0 h	2.38	10.9	0.00
12.0 h	59.0	150	0.00

Table 13

1. LISTING OF ADVERSE EVENTS

50mg Fasting Study

Subject	Specification orig. term	Specification pref. term	Serious	Date of Onset	Time of Onset	Date ceased	Time ceased	Most severe intensity	Relationship to test drug	Frequency	Action taken for Event	Outcome
1	dizziness	dizziness	No	29/02/96	11:50	29/02/96	14:30	mild	poss.	cont.	none	res. no seq.
9	dizziness	dizziness	No	29/02/96	9:50	29/02/96	20:10	mild	poss.	interm.	none	res. no seq.
32	syncope	syncope	No	06/03/96	8:00	06/03/96	.	mod.	unrel.	cont.	other	res. no seq.
40	headache	headache	No	06/03/96	18:10	06/03/96	20:00	mod.	rem.	cont.	other	res. no seq.

Subject	Treatment for Event orig. term	Treatment for Event pref. term	Start of admin.	Drug regimen	Time of admin.	Route of admin.	End of admin.
1	.	.	.	.	.	.	.
9	.	.	.	.	8.03-8.30h	i.v.	06/03/96
32	NaCl 0.9% i.v. (500 ml)	NaCl 0.9%	06/03/96	1 x 1	18.50h	p.o.	06/03/96
40	paracetamol (Panadol®) 0.5 g tabl.	paracetamol	06/03/96				

Subject	Comment
32	Before the drug administration she fell down from the chair and became unconscious for a short time (about 4 sec).

Appendix E

5. MEAN PHARMACOKINETIC PARAMETERS OF DICLOFENAC

Treatment A: Diclofenac-Na 50 mg, delayed release tablet (Ratiopharm); batch no.: 960103.

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)				1129.5		1141.4	646.2		57
t_{max} (h)	1.9	0.8		1.50	40				
$t_{½}$ (h)	1.05	0.36		0.98	34				
k_{el} (1/h)	0.73	0.23		0.71	32				
R ass. with k_{el}				0.963					
n ass. with R				5					
AUC_{0-t} (ng.h/ml)				1028		1013	409		40
$AUC_{0-\infty}$ (ng.h/ml)				1075		1053	412		39
F_{rel}				1.02		0.98	0.42		43
MRT_{0-t} (h)	2.33	0.81		2.20	35				

Treatment B: Voltaren® 50 mg, delayed release tablet as reference; batch no.: LT4101.

	Arithmetic					Geometric			
	Mean	SD	95% C.I. of the mean lower limit - upper limit	Median	CV (%)	Mean	SD	95% C.I. of the mean lower limit - upper limit	CV (%)
C_{max} (ng/ml)				1105.8		1071.8	573.6		54
t_{max} (h)	1.8	0.7		1.50	42				
$t_{½}$ (h)	1.01	0.55		0.82	54				
k_{el} (1/h)	0.88	0.45		0.85	51				
R ass. with k_{el}				0.980					
n ass. with R				5					
AUC_{0-t} (ng.h/ml)				1030		1038	393		38
$AUC_{0-\infty}$ (ng.h/ml)				1054		1078	392		36
MRT_{0-t} (h)	2.24	0.74		2.21	33				

Appendix D

2. MEAN PLASMA CONCENTRATIONS OF DICLOFENAC

Plasma concentrations of diclofenac (ng/ml)

Treatment A: Diclofenac-Na 50 mg, delayed release tablet (Ratiopharm); batch no.: 960103.

	Mean	SD	Median
baseline	0.00	0.00	0.00
0.5 h	1.34	9.22	0.00
1.0 h	209	484	0.00
1.5 h	571	675	383
2.0 h	536	611	361
2.25 h	386	440	234
2.5 h	314	415	163
2.75 h	235	290	129
3.0 h	200	357	105
3.25 h	162	254	73.7
3.5 h	129	216	62.1
4.0 h	109	289	47.0
4.5 h	66.0	134	34.0
5.0 h	34.5	56.6	26.6
5.5 h	24.7	36.8	21.2
6.0 h	11.6	30.8	0.00
7.0 h	2.92	9.90	0.00
8.0 h	1.03	4.98	0.00
10.0 h	0.223	1.53	0.00
12.0 h	0.00	0.00	0.00

Plasma concentrations of diclofenac (ng/ml)

Treatment B: Voltaren® 50 mg, delayed release tablet as reference; batch no.: LT4101.

	Mean	SD	Median
baseline	0.600	4.11	0.0
0.5 h	119	476	0.0
1.0 h	316	568	0.0
1.5 h	449	529	286
2.0 h	451	426	334
2.25 h	408	453	274
2.5 h	345	307	232
2.75 h	334	466	174
3.0 h	234	302	130
3.25 h	155	163	101
3.5 h	111	88.4	80.5
4.0 h	74.4	73.1	51.0
4.5 h	52.5	57.8	36.4
5.0 h	26.6	26.6	24.7
5.5 h	15.7	18.1	0.0
6.0 h	9.90	15.3	0.0
7.0 h	1.71	6.80	0.0
8.0 h	0.439	3.01	0.0
10.0 h	0.00	0.00	0.0
12.0 h	0.00	0.00	0.0