# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 65-156

# BIOEQUIVALENCE REVIEW(S)

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 65-156 |
| **Drug Product Name** | Minocycline Hydrochloride Tablets USP |
| **Strength** | 50 mg, 75 mg, 100 mg |
| **Applicant Name** | Ranbaxy Pharmaceuticals Inc. |
| **Address** | 600 College Road East, Princeton, New Jersey 08540 |
| **Submission Date(s)** | February 10, 2003 |
| **Amendment Date(s)** | August 12, 2003 |
| **Reviewer** | Lin-Whei Chuang |
| **First Generic** | No |
| **File Location** | V:\FIRMSNZ\RANBAXY\LTRS&REV\65156N0203.doc |

## I. Executive Summary

This application for minocycline hydrochloride tablets references Minocin Capsules. At the time of submission there were no reference drug for minocycline hydrochloride tablet in the Orange Book and the Agency determined that the withdrawal of minocin tablet from sale was not due to safety or efficacy reasons. The application includes one fasted and one fed BE study. The fasting study is a single-dose two-way crossover study using 28 male and female normal healthy volunteers given a dose of 100 mg in tablet or capsule dosage from. The results (point estimate, 90% CI) of the fasting BE study are LAUCt of 1.06, 101-111%; LAUCi of 1.06, 101-110%; and LCmax of 1.12, 105-119%. The fed BE study is a single-dose two-way crossover study using 24 male and female normal healthy volunteers given a dose of 100 mg in tablet or capsule dosage form. The results of the fed BE study are LAUCt of 0.94, 91-96%; LAUCi of 0.94, 91-97%; and LCmax of 1.00, 96-103%. These studies are acceptable. The dissolution (900 mL of water, paddle at 50 rpm) testing is incomplete. There is now a tablet RLD for this product. Therefore, the firm needs to repeat the dissolution testing for all 3 strengths comparing its test products with the current RLD, Medicis' (PAR's) minocycline hydrochloride tablets, 50 mg, 75 mg and 100 mg. The test formulations of the 50 mg, 75 mg, and 100 mg tablets are proportionally similar. The waiver request of in vivo BE requirements for the 50 mg and 75 mg tablets is pending.

## II. Table of Contents

## III. Submission Summary

### A. Drug Product Information

| | |
|---|---|
| **Test Product** | Minocycline HCl Tablet, 50 mg, 75 mg and 100 mg |
| **Reference Product** | The reference drugs used in this ANDA are Minocin pellet-filled capsules, 50 mg and 100 mg, and Watson's Dynacin 75 mg capsule. |
| **RLD Manufacturer** | Lederle Pharmaceutical Division manufactured Minocin capsules for Wyeth Pharms Inc.<br>Watson Labs manufactured Dynacin for Medicis, The Dermatology Company. |
| **NDA No.** | 50649 and ANDA #63065 |
| **RLD Approval Date** | Minocin 50 mg and 100 mg capsules were approved on 5/31/1990l and Minocin 75 mg capsule was approved on 2/12/2001. However, according to the PDR at the time of the current submission, Minocin was only available in the 50 mg and 100 mg strengths. Therefore Dynacin 75 mg capsule of Watson (approved on 6/10/1999 through ANDA #63065) was used for the comparative dissolution testing. However, the current RLD in the Orange Book is PAR's (sold to Medicis in 8/2003) Minocycline HCl 100 mg Tablets, approved 4/16/03. Medicis also manufactures Minocycline 50 mg and 75 mg tablets. |
| **Indication** | Treatment of infections caused by microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug. |

## B. PK/PD Information

| | |
|---|---|
| **Bioavailability** | 58-100% |
| **Food Effect** | AUC was not noticeably influenced; Cmax was slightly decreased (11.2%); and Tmax was delayed by 1 hour. |
| **Tmax** | 2.1 hours (1-4 hours) |
| **Metabolism** | No metabolites have been reported. |
| **Excretion** | Excreted somewhat into the bile and not reabsorbed completely in the intestine. |
| **Half-life** | 15.5 hours (11.1 –22.1 hours) |
| **Relevant OGD or DBE History** | Minocin tablets (NDA 50-451), manufactured by Lederle, were withdrawn from the market in 1996. The withdrawal from sale was not due to safety or efficacy reasons (Federal Register 1998 Jan 27; Vol. 63(17): 3903-3904).<br>The DBE first approved the use of Lederle's Minocin 100 mg capsules as the reference product for generic minocycline HCl tablet products in the review of the protocol P #98-014 (Stiefel Laboratories; 04/13/1998) and then in ANDA #65-131 (Par Pharmaceutical on 5/31/2002). Par's minocycline tablets were approved on 4/16/2003* and became the RLD in 4/2003. This product was sold to Medicis in 8/2003.<br>The firm (Ranbaxy) had submitted Control Document #01-046 on 1/17/2001 requesting the OGD's recommendation on the BE requirements for the test products. OGD's letter of 5/14/2001 states that, in addition to the comments in Federal Register, the firm may request waivers for its 50 mg and 75 mg tablets provided the BE studies on the 100 mg tablet are acceptable, the lower strength formulations are proportionally similar to the highest strength and they meet the dissolution specification. However, the OGD also states that if Lederle reintroduces the 100 mg tablet to the market the firm may have to conduct another BE study to maintain the firm's existing regulatory status (AB rating). |
| **Agency Guidance** | None |
| **Drug Specific Issues (if any)** | None |



* = Par conducted fasted and fed studies and comparative dissolution using Minocin capsules as RLD. The fasted study is a single-dose two-way crossover study using 28 male normal healthy volunteers given a dose of 100 mg. The results (point estimate and 90% CI) of the fasted BE study are LAUCt of 1.01, 97-106%; LAUCi of 1.0, 96-105%; and LCmax of 1.03, 98-109%. The fed study is a single-dose two-way crossover study using 23 male normal healthy volunteers given a dose of 100 mg. The point estimates of the fed BE study are LAUCt 0.94; LAUCi 0.94; and LCmax of 0.99. The fasted and fed studies are acceptable. The firm also conducted acceptable comparative dissolution testing using the USP method (Paddle at 50 rpm in 900 mL of water) and met the USP tolerance of NLT 75%(Q) in 45 min..

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## C. Contents of Submission

| Study Types | Yes/No? | How many? |
|---|---|---|
| Single-dose fasting | Yes | 1 |
| Single-dose fed | Yes | 1 |
| Steady-state | No | 0 |
| In vitro dissolution | Yes | 3 |
| Waiver requests | Yes | 2 |
| BCS Waivers | No | 0 |
| Vasoconstrictor Studies | No | 0 |
| Clinical Endpoints | No | 0 |
| Failed Studies | No | 0 |
| Amendments | No | 0 |

## D. Pre-Study Bioanalytical Method Validation

| | Parent | Metabolite | Metabolite2 |
|---|---|---|---|
| | | N/A | |
| Analyte name | | | |
| Internal Standard | | | |
| Method description | | | |
| QC range (ng/mL) | | | |
| Standard curve range (ng/mL) | | | |
| Limit of quantitation (ng/mL) | | | |
| Average recovery of Drug (%) | | | |
| Average Recovery of Int. Std (%) | | | |
| Intraday precision range (%CV) | | | |
| Intraday accuracy range (%) | | | |
| Interday precision range (%CV) | | | |
| Interday accuracy range (%) | | | |
| Bench-top stability (hrs) | | | |
| Stock stability (days) | | | |
| Processed stability (hrs) | | | |
| Freeze-thaw stability (cycles) | | | |
| Long-term storage stability (days) | | | |
| Dilution integrity | | | |
| Specificity | | | |
| SOPs submitted | | | |
| Bioanalytical method is acceptable | | | |
| included (Y/N) | | | |
| Random Selection of Serial Chromatograms | | | |

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Comment on the Bioanalytical Method:
The firm should be advised that in future submissions, for pivotal BE studies for marketing, chromatograms from 20% serially selected subjects should be included (Please refer to *Guidance for Industry: Bioanalytical Method Validation, 5/2001*).

**E. In Vivo Studies**

1. Single-dose Fasting Bioequivalence Study

| Study Summary | |
|---|---|
| **Study No.** | AAI-US-134 |
| **Study Design** | Single-dose 2-way crossover |
| **No. of subjects enrolled** | 28 |
| **No. of subjects completing** | 28 |
| **No. of subjects analyzed** | 28 |
| **Subjects (Normal/Patients?)** | Normal |
| **Sex(es) included (how many?)** | Male: 16 Female: 12 |
| **Test product** | Minocycline HCl Tablet |
| **Reference product** | Minocin Capsule |
| **Strength tested** | 100 mg |
| **Dose** | 100 mg |

| Summary of Statistical Analysis<br>Additional Information in Appendix, Table and Table 2 | | |
|---|---|---|
| **Parameter** | **Point Estimate** | **90% Confidence Interval** |
| **$AUC_{0-t}$** | 1.06 | 1.011 – 1.106 |
| **$AUC_{\infty}$** | 1.06 | 1.01 – 1.101 |
| **$C_{max}$** | 1.12 | 1.052 – 1.192 |

| Reanalysis of Study Samples<br>Additional information in Appendix, Table | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Reason why assay was repeated** | **Number of samples reanalyzed** | | | | **Number of recalculated values used after reanalysis** | | | |
| | **Actual number** | | **% of total assays** | | **Actual number** | | **% of total assays** | |
| | **T** | **R** | **T** | **R** | **T** | **R** | **T** | **R** |
| None had to be re-assayed because of PK anomaly. | | | | | | | | |
| **Total** | | | | | | | | |

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Did use of recalculated plasma concentration data change study outcome? N/A

**Comments on Fasting Study:**
The fasting study is acceptable.

2. Single-dose Fed Bioequivalence Study

| | |
|---|---|
| **Study No.** | AAI-US-135 |
| **Study Design** | Single-dose 2-way crossover |
| **No. of subjects enrolled** | 24 |
| **No. of subjects completing** | 24 |
| **No. of subjects analyzed** | 24 |
| **Subjects (Normal/Patients?)** | Normal |
| **Sex(es) included (how many?)** | Male: 17 Female: 7 |
| **Test product** | Minocycline HCl Tablet |
| **Reference product** | Minocin Capsule |
| **Strength tested** | 100 mg |
| **Dose** | 100 mg |

| **Summary of Statistical Analysis Additional Information in Appendix, Table 3 and Table 4** | | |
|---|---|---|
| **Parameter** | **Point Estimate** | **90% Confidence Interval** |
| **$AUC_{0-t}$** | 0.94 | 0.907 – 0.964 |
| **$AUC_{\infty}$** | 0.94 | 0.906 – 0.967 |
| **$C_{max}$** | 1.00 | 0.962 – 1.033 |

| **Reanalysis of Study Samples Additional information in Appendix, Table** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Reason why assay was repeated** | **Number of samples reanalyzed** | | | | **Number of recalculated values used after reanalysis** | | | |
| | **Actual number** | | **% of total assays** | | **Actual number** | | **% of total assays** | |
| | **T** | **R** | **T** | **R** | **T** | **R** | **T** | **R** |
| None had to be re-assayed. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Did use of recalculated plasma concentration data change study outcome? N/A

**Comments on fed study:**
The fed study is acceptable.

F. Formulation

| | |
|---|---|
| **Location in appendix** | Section B, Page 25 |
| **Inactive ingredients within IIG Limits (yes or no)** | **Yes** |
| **If no, list ingredients outside of limits** | **N/A** |
| **If a tablet, is the product scored? (yes or no)** | **Yes** |
| **If yes, which strengths are scored?** | **100 mg** |
| **Is scoring of RLD the same as test? (yes or no)** | **No, the RLD (Par's tablets) are not scored.** |
| **Formulation is acceptable (yes or no)** | **Yes** |
| **If not acceptable, why?** | **N/A** |

**[NOTE: The Chemistry reviewer is aware of the difference in the scoring configuration between the test product and the current RLD.]**

G. In Vitro Dissolution

| | |
|---|---|
| **Source of Method** | USP |
| **Medium** | Water |
| **Volume (mL)** | 900 |
| **USP Apparatus type** | II (Paddle) |
| **Rotation (rpm)** | 50 |
| **Firm's proposed specifications** | N/A |
| **FDA-recommended specifications** | NLT 75% (Q) in 45 minutes |
| **F2 metric calculated (yes or no)** | No |
| **If no, reason why F2 not calculated** | The test drugs are fast-dissolving (>100% are dissolved in 10 min.) |
| **Method is acceptable (yes or no)** | Yes |
| **Testing Site** | Ohm Laboratories Inc., PO Box 7387, 1385 Livingston Avenue, New Brunswick, New Jersey 08902 |

| **F2 metric, other strengths compared to biostudy strength** | | | |
|---|---|---|---|
| Low strength | Highest strength | F2 metric for test | F2 metric for RLD |
| N/A | | | |

| **F2 metric, test compared to reference** | |
|---|---|
| Strength | F2 metric |
| N/A | |

Comments on Dissolution Testing:
The firm used Minocin capsules, 50 mg and 100 mg, and Dynacin 75 mg capsule as the reference drugs. The firm needs to repeat the dissolution testing for all 3 strengths comparing its test products with the current RLD, Medicis' minocycline tablets approved through Par's ANDA #65-131 on 4/16/2003. The F2 metrics should be calculated comparing lower strengths to the highest strength and the test to the reference for each strength.

**H. Waiver Request(s)**

| | |
|---|---|
| Strengths for which waivers requested | 50 mg, 75 mg |
| Regulation cited | Yes, 21 CFR 320.22(d)(2) |
| Proportional to strength tested in vivo (yes or no) | Yes |
| Dissolution is acceptable (yes or no) | No [incomplete, need to repeat] |
| Waiver granted (yes or no) | No |

**I. Deficiency Comments:**

The firm needs to repeat the dissolution testing for all 3 strengths comparing its test products with the current RLD, Medicis' minocycline tablets, 50 mg, 75 mg and 100 mg. The F2 metrics should be calculated comparing lower strengths to the highest strength and the test to the reference for each strength.

**J. Recommendations**

1. The fasting and non-fasting bioequivalence studies conducted by Ranbaxy Pharmaceuticals Inc. on its minocycline hydrochloride 100 mg tablets, lot #73400201, comparing it to Minocin 100 mg capsule, lot #3013510, have been found acceptable by the Division of Bioequivalence. However, the firm should be advised that in future submissions, for pivotal BE studies for marketing, [redacted] serially selected subjects should be included (Please refer to *Guidance for Industry: Bioanalytical Method Validation, 5/2001*).

2. The comparative dissolution tests conducted by Ranbaxy Pharmaceuticals Inc. on its minocycline hydrochloride 50 mg, 75 mg and 100 mg tablets, comparing them to Minocin 50 mg and 100 mg capsule, and Dynacin 75 mg capsule have been found incomplete by the Division of Bioequivalence. The firm is advised to repeat the dissolution testing for all 3 strengths comparing its test products with the current RLD (Medicis' Minocycline Tablets, 50 mg, 75 mg and 100 mg) in 900 mL of water using USP Apparatus II (paddle) at 50 rpm. The F2 metrics should be calculated comparing lower strengths to the highest strength and the test to the reference for each strength.

Lin-Whei Chuang 10/15/2003

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG Date: 10/15/2003

for Barbara M. Davit 10/15/03

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

# IV. Appendix

## A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

| **Study Information** | |
|---|---|
| **Study Number** | [redacted]-US-134 |
| **Study Title** | Single Dose Two-Way Crossover Fasted Bioequivalence Study of Minocycline 100 mg Capsules in Healthy Volunteers.* |
| **Clinical Site** | [redacted] |
| **Principal Investigator** | [redacted] |
| **Study/Dosing Dates** | 10/27/2002 & 11/03/2002 |
| **Analytical Site** | [redacted] |
| **Analytical Director** | [redacted] |
| **Analysis Dates** | 10/30/2002-11/23/2002 |
| **Storage Period (no. of days from first sample to final analysis)** | 27 |

* = The firm erroneously identified the study drugs as capsules in the study title, however, in the content of the protocol, the test product was correctly identify as tablet and the reference drug as capsule.

| | | |
|---|---|---|
| **Treatment ID** | A | B |
| **Test or Reference** | Test | Reference |
| **Product Name** | Minocycline HCl Tablet | Minocin Capsule |
| **Manufacturer** | Ranbaxy | Lederle |
| **Batch/Lot No.** | 73400201 | 3013510 |
| **Manufacture Date** | 09/2002 | N/A |
| **Expiration Date** | N/A | 01/2004 |
| **Strength** | 100 mg | 100 mg |
| **Dosage Form** | Tablet | Capsule |
| **Batch Size** | [redacted] tablets | N/A |
| **Production Batch Size** | [redacted] tablets | N/A |
| **Potency** | 98.8% | 96.7% |
| **Content Uniformity** | 102.0% (95.5-103.9%) | 96.7% (96-99.2%) |
| **Formulation** | See Appendix Section B | |
| **Dose Administered** | 100 mg | 100 mg |
| **Route of Administration** | Oral | Oral |

| | |
|---|---|
| **No. of Sequences** | 2 |
| **No. of Periods** | 2 |
| **No. of Treatments** | 2 |
| **No. of Groups** | 1 |
| **Washout Period** | 7 days |
| **Randomization Scheme** | AB for #1, 3, 5-7, 9, 12, 15, 20, 21, 23, 25, 27, 28 and BA for the rest of 28 subjects. |
| **Blood Sampling Times** | 0, 0.25, 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 48, 60, 72 hours post-dose. |
| **Blood Volume Collected/Sample** | 10 mL |
| **Blood Sample Processing/Storage** | Centrifugation to obtain plasma and stored at –20°C within 1 hour until transfer to analytical site. |
| **IRB Approval** | Yes, by [redacted] on 10/14/2002. |
| **Informed Consent** | Yes, by [redacted] on 10/17/2002. |
| **Subjects Demographics** | See Table 1 |
| **Length of Fasting** | From 10 hours pre-dose to 4 hours post-dose. |
| **Length of Confinement** | From evening before dosing to 24 hours post-dose. |
| **Safety Monitoring** | Vital signs were obtained prior dosing and a physician was present for at least 4 hours post-dose. |

**Table 1 Demographics of Study Subjects**

| Age (yr.) | | Weight (lb) | | Age Groups | | Gender | | Race | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Range | % | Sex | % | Category | % |
| | | | | <18 | 0 | | | Caucasian | 57.1 |
| Mean | 27.7 | Mean | 162.4 | 18-40 | 96.4 | Male | 57.1 | Afr. Amer. | 35.7 |
| SD | 6.2 | SD | 23 | 41-64 | 3.6 | Female | 42.9 | Hispanic | 3.6 |
| Range | 20-43 | Range | 128-213 | 65-75 | 0 | | | Asian | 3.6 |
| | | | | >75 | 0 | | | Others | 0 |

**Study Results**

**Table 2 Dropout Information**

**Subject No** None
**Reason**
**Period**
**Replacement**

**Was there a difference in side effects for the test versus the reference?**

Please see Adverse events below.

**Table 3 Study Adverse Events**

| Adverse Event Description | # in Test Group | # in Reference Group |
|---|---|---|
| Headache | 1 | 0 |
| Lightheadedness | 0 | 1 |
| Vasovagal Reaction | 1 | 0 |
| **Total:** | 2 | 1 |

**Comments:** (*on adverse events)*

**Was there a difference in protocol deviations for the test versus the reference?**
**No**

**Table 4 Protocol Deviations**

| **Type** | **Subject #s (Test)** | **Subject #s (Reference)** |
|---|---|---|
| None reported | | |

**Comments:** (*indicate whether protocol deviations compromised the integrity of study*)
No

**Table 5 Assay Validation – Within Study**

| | Parent | Metabolite |
|---|---|---|
| **QC Conc. (ng/mL)** | | N/A |
| **Inter day Precision (%CV)** | | |
| **Inter day Accuracy (%)** | | |
| | | |
| **Cal. Standards Conc. (ng/mL)** | | N/A |
| **Inter day Precision (%CV)** | | |
| **Inter day Accuracy (%)** | | |
| **Linearity Range (range of $R^2$ values)** | | |

**Chromatograms:** Any interfering peaks?
None

**Table 6 SOP's dealing with analytical repeats of study samples**

| SOP No. | Date of SOP | SOP Title |
|---|---|---|
| MA492 | 11/26/2002 | Reason for Repetition; and Reason for Acceptance (p. 0455, Vol. 1.3). |
| | | |

**Comments on repeat assays.**
None had to be repeated due to PK anomaly.

- Identify which SOP's were not followed, as well as which subjects, treatment, and sampling times were involved. None
- Did recalculation of plasma concentrations change the study outcome? N/A
- Does the reviewer agree with the outcome of the repeat assays? If no, explain reason(s). N/A
- Provide any other comments about repeat assays. None

**Comments on Within-Study Validation:**
The range of Cmax was 692-2920 ng/mL, therefore a QC range of [redacted], is acceptable.

**Conclusion:** Analytical method is acceptable

**Table 7 Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in Table 10 and Figure 1

| | TEST MEAN | SD | REF. MEAN | SD | TEST/REF. |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI (NG*HR/ML) | 31846.07 | 9406.77 | 30654.90 | 10455.88 | 1.04 |
| AUCT (NG*HR/ML) | 30158.79 | 8379.72 | 28938.39 | 9385.09 | 1.04 |
| CMAX (NG/ML) | 1753.29 | 470.94 | 1603.89 | 552.99 | 1.09 |

| | | | | | |
|---|---|---|---|---|---|
| KE | 0.05 | 0.01 | 0.05 | 0.01 | 1.02 |
| LAUCI* | 30587.25 | 0.29 | 29008.67 | 0.34 | 1.05 |
| LAUCT* | 29085.52 | 0.27 | 27504.79 | 0.33 | 1.06 |
| LCMAX* | 1692.84 | 0.27 | 1511.38 | 0.36 | 1.12 |
| THALF (HR) | 15.66 | 3.73 | 15.98 | 3.61 | 0.98 |
| TMAX (HR) | 1.61 | 0.55 | 2.20 | 0.72 | 0.73 |

* = GEOMETRIC MEANS AND RATIO OF GEOMETRIC MEANS

**Table 2 Least Square Geometric Means and 90% Confidence Intervals**

| | TEST LSMEAN | REF. LSMEAN | TEST/REF. | 90% CONF. INT. |
|---|---|---|---|---|
| PARAMETER | | | | |
| LAUCI | 30587.25 | 29008.67 | 1.05 | 100.97 - 110.11 |
| LAUCT | 29085.52 | 27504.79 | 1.06 | 101.12 - 110.58 |
| LCMAX | 1692.84 | 1511.38 | 1.12 | 105.20 - 119.25 |

**Table 9 Additional Study Information**

| | | |
|---|---|---|
| **Root mean square error, $AUC_{0-t}$** | 0.098132 | |
| **Root mean square error, $AUC_{\infty}$** | 0.095112 | |
| **Root mean square error, $C_{max}$** | 0.137438 | |
| **mean ratio $AUC_{0-t}/AUC_{\infty}$** | T = 0.95 | R = 0.95 |
| **Range of values, ratio $AUC_{0-t}/AUC_{\infty}$** | T = 0.81 – 0.98 | R = 0.81 – 0.98 |

**Comments:** (on pharmacokinetic analysis)

- $k_{el}$ and $AUC_{\infty}$ were determined for all subjects.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: 35.6 ng/mL for #7, period 2 (treatment B) which was confirmed in re-assay.
  b. first scheduled post-dose sampling time as Tmax: None
  c. first measurable drug concentration as $C_{max}$: None

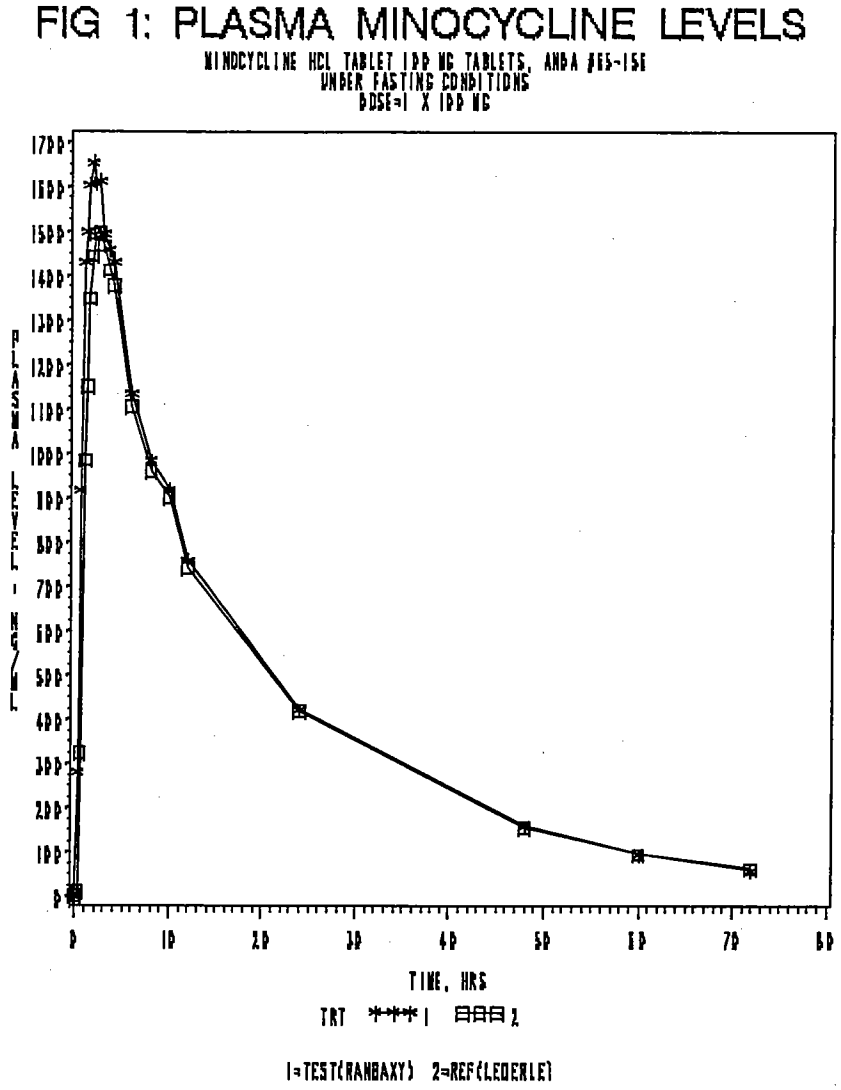
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? If so, did these affect the integrity of the study? No
- Are the 90% confidence intervals for $AUC_{0-t}$, $AUC_{\infty}$, $C_{max}$ within the acceptable limits of 80-125%? Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. N/A

**Conclusion:** The single-dose fasting bioequivalence study is acceptable.

**Table 10 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

| | TEST MEAN | SD | REF. MEAN | SD | TEST/REF. |
|---|---|---|---|---|---|
| TIME (HR) | (N=28) | | (N=28) | | |
| 0 | 0.000 | 0.000 | 1.271 | 6.728 | 0.000 |
| 0.25 | 280.004 | 253.514 | 11.796 | 23.525 | 23.736 |
| 0.5 | 916.429 | 414.857 | 325.171 | 169.193 | 2.818 |
| 1 | 1431.143 | 365.376 | 985.929 | 297.350 | 1.452 |
| 1.25 | 1496.964 | 377.441 | 1151.464 | 382.132 | 1.300 |
| 1.5 | 1604.250 | 456.793 | 1348.571 | 436.218 | 1.190 |
| 1.75 | 1654.750 | 447.467 | 1444.929 | 485.832 | 1.145 |
| 2 | 1606.286 | 447.550 | 1494.714 | 497.919 | 1.075 |
| 2.5 | 1613.429 | 486.794 | 1496.214 | 526.140 | 1.078 |
| 3 | 1492.607 | 429.417 | 1465.714 | 516.978 | 1.018 |
| 3.5 | 1457.286 | 432.064 | 1413.250 | 472.513 | 1.031 |
| 4 | 1432.286 | 430.391 | 1378.857 | 490.290 | 1.039 |
| 6 | 1136.929 | 312.466 | 1106.464 | 365.592 | 1.028 |
| 8 | 983.357 | 246.494 | 961.286 | 296.026 | 1.023 |
| 10 | 918.393 | 237.537 | 901.750 | 278.380 | 1.018 |
| 12 | 760.321 | 196.060 | 741.714 | 225.040 | 1.025 |
| 24 | 422.893 | 132.091 | 419.357 | 147.590 | 1.008 |
| 48 | 158.314 | 78.464 | 155.711 | 83.819 | 1.017 |
| 60 | 95.839 | 57.750 | 95.021 | 59.304 | 1.009 |
| 72 | 60.636 | 48.575 | 63.104 | 48.123 | 0.961 |

**Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

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2. Single-dose Fed Bioequivalence Study

| **Study Information** | |
|---|---|
| **Study Number** | AAI-US-135 |
| **Study Title** | Single Dose Two-Way Crossover Fed Bioequivalence Study of Minocycline 100 mg Capsules in Healthy Volunteers.* |
| **Clinical Site** | [redacted] |
| **Principal Investigator** | [redacted] |
| **Study/Dosing Dates** | 11/09/2002 & 11/16/2002 |
| **Analytical Site** | [redacted] |
| **Analytical Director** | [redacted] |
| **Analysis Dates** | 11/28/2002-12/06/2002 |
| **Storage Period (no. of days from first sample to final analysis)** | 27 |

* = The firm erroneously identified the study drugs as capsules in the study title, however, in the content of the protocol, the test product was correctly identify as tablet and the reference drug as capsule.

| **Treatment ID** | A | B |
|---|---|---|
| **Test or Reference** | Test | Reference |
| **Product Name** | Minocycline HCl Tablet | Minocin Capsule |
| **Manufacturer** | Ranbaxy | Lederle |
| **Batch/Lot No.** | 73400201 | 3013510 |
| **Manufacture Date** | 09/2002 | N/A |
| **Expiration Date** | N/A | 01/2004 |
| **Strength** | 100 mg | 100 mg |
| **Dosage Form** | Tablet | Capsule |
| **Batch Size** | [redacted] tablets | N/A |
| **Production Batch Size** | [redacted] tablets | N/A |
| **Potency** | 98.8% | 96.7% |
| **Content Uniformity** | 102.0% (95.5-103.9%) | 96.7% (96-99.2%) |
| **Formulation** | See Appendix Section B | |
| **Dose Administered** | 100 mg | 100 mg |
| **Route of Administration** | Oral | Oral |

| | |
|---|---|
| **No. of Sequences** | 2 |
| **No. of Periods** | 2 |
| **No. of Treatments** | 2 |
| **No. of Groups** | 1 |
| Washout Period | 7 days |
| **Randomization Scheme** | AB for #2, 3, 7, 8, 13-17, 21-23 and BA for the rest of 24 subjects. |
| **Blood Sampling Times** | 0, 0.25, 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 48, 60, 72 hours post-dose. |
| **Blood Volume Collected/Sample** | 10 mL |
| **Blood Sample Processing/Storage** | Centrifugation to obtain plasma and stored at –20°C within 1 hour until transfer to analytical site. |
| **IRB Approval** | Yes, by [redacted] on 10/14/2002. |
| **Informed Consent** | Yes, by [redacted] on 10/24/2002. |
| **Subjects Demographics** | See Table 11 |
| **Length of Fasting** | From 10 hours pre-dose to 4 hours post-dose. |
| **Length of Confinement** | From evening before dosing to 24 hours post-dose. |
| **Safety Monitoring** | Vital signs were obtained prior dosing and a physician was present for at least 4 hours post-dose. |

**Table 11 Demographics of Study Subjects**

| Age (Year) | | Weight (lb) | | Age Groups | | Gender | | Race | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Range | % | Sex | % | Category | % |
| | | | | <18 | 0 | | | Caucasian | 62.5 |
| Mean | 27.5 | Mean | 161.5 | 18-40 | 95.8 | Male | 70.8 | Afr. Amer. | 25.0 |
| SD | 6.8 | SD | 24.7 | 41-64 | 4.2 | Female | 29.2 | Hispanic | 0 |
| Range | 18-45 | Range | 111-200 | 65-75 | 0 | | | Asian | 4.2 |
| | | | | >75 | 0 | | | Others | 8.3 |

**Study Results**

**Table 12 Dropout Information**

| | |
|---|---|
| **Subject No** | None |
| **Reason** | |
| **Period** | |
| **Replacement** | |

**Was there a difference in side effects for the test versus the reference?**
**Please see Adverse Events below.**

**Table 13 Study Adverse Events**

| Adverse Event Description | # in Test Group | # in Reference Group |
|---|---|---|
| Headache | 3 | 0 |
| Nausea | 1 | 0 |
| Cough | 1 | 0 |
| Sneezing | 1 | 0 |
| Rhinorrhea | 1 | 0 |
| Pyrexia | 1 | 0 |
| Syncope | 0 | 1 |
| **Total:** | **8** | **1** |

**Comments:** *(on adverse events)*
All adverse events reported had none or remote relationship to the study drugs.

**Was there a difference in protocol deviations for the test versus the reference?**

The adverse events occurred more frequent in the test treatment than the reference treatment, however, they had none or remote relationship to the study drugs.

**Table 14 Protocol Deviations**

| Type | Subject #s (Test) | Subject #s (Reference) |
|---|---|---|
| No significant deviations were reported | | |

**Comments**: *(indicate protocol deviations compromised the integrity of study)*
N/A

**Table 15 Assay Validation – Within Study**

| | Parent | Metabolite |
|---|---|---|
| **QC Conc. (ng/mL)** | | N/A |
| **Inter day Precision (%CV)** | | |
| **Inter day Accuracy (% Accuracy)** | | |
| | | |
| **Cal. Standards Conc. (ng/mL)** | | N/A |
| **Inter day Precision (%CV)** | | |
| **Inter day Accuracy (% Accuracy)** | | |
| **Linearity Range (range of $R^2$ values)** | | |

**Chromatograms:** Any interfering peaks? No

**Table 16 SOP's dealing with analytical repeats**

| SOP No. | Date of SOP | SOP Title |
|---|---|---|
| MA492* | 11/26/2002 | Reason for Repetition; and Reason for Acceptance (p. 0455, Vol. 1.3). |

* = No samples were repeated.

**Comments on repeat assays.**

- Identify which SOP's were not followed, as well as which subjects, treatment, and sampling times were involved. None
- Did recalculation of plasma concentrations change the study outcome? N/A
- Does the reviewer agree with the outcome of the repeat assays? If no, explain reason(s). N/A
- Provide any other comments about repeat assays. None

**Comments on Within-Study Validation:**
The range of Cmax was 963-1870 ng/mL, therefore a QC range of [redacted] is acceptable.

**Conclusion:** Analytical method is acceptable.

**Table 17 Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in Table 20 and Figure 2

| | TEST MEAN | SD | REF. MEAN | SD | TEST/REF. |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI (NG*HR/ML) | 25046.59 | 4569.92 | 26839.14 | 5249.46 | 0.93 |
| AUCT (NG*HR/ML) | 23868.58 | 4208.66 | 25592.91 | 4908.80 | 0.93 |
| CMAX (NG/ML) | 1310.13 | 203.31 | 1316.38 | 221.81 | 1.00 |
| KE | 0.05 | 0.01 | 0.05 | 0.01 | 0.99 |
| LAUCI | 24636.58 | 0.19 | 26341.75 | 0.20 | 0.94 |
| LAUCT | 23501.64 | 0.18 | 25135.15 | 0.20 | 0.94 |
| LCMAX | 1294.83 | 0.16 | 1299.16 | 0.16 | 1.00 |
| THALF (HR) | 15.48 | 1.86 | 15.38 | 2.11 | 1.01 |
| TMAX (HR) | 2.40 | 1.03 | 3.81 | 0.98 | 0.63 |

**Table 18 Geometric Means and 90% Confidence Intervals**

| | TEST LSMEAN | REF. LSMEAN | TEST/REF. | 90% CONF. INT. |
|---|---|---|---|---|
| PARAMETER | | | | |
| LAUCI | 24636.58 | 26341.75 | 0.94 | 90.56 - 96.59 |
| LAUCT | 23501.64 | 25135.15 | 0.94 | 90.72 - 96.37 |
| LCMAX | 1294.83 | 1299.16 | 1.00 | 96.19 - 103.27 |

**Table 19 Additional Study Information**

| | | |
|---|---|---|
| **Root mean square error, $AUC_{0-t}$** | 0.060987 | |
| **Root mean square error, $AUC_{\infty}$** | 0.065047 | |
| **Root mean square error, $C_{max}$** | 0.071588 | |
| **mean ratio $AUC_{0-t}/AUC_{\infty}$** | T = 0.95 | R = 0.95 |
| **Range of values, ratio $AUC_{0-t}/AUC_{\infty}$** | T = 0.92 – 0.97 | R = 0.91 – 0.98 |

**Comments:** (on pharmacokinetic analysis)

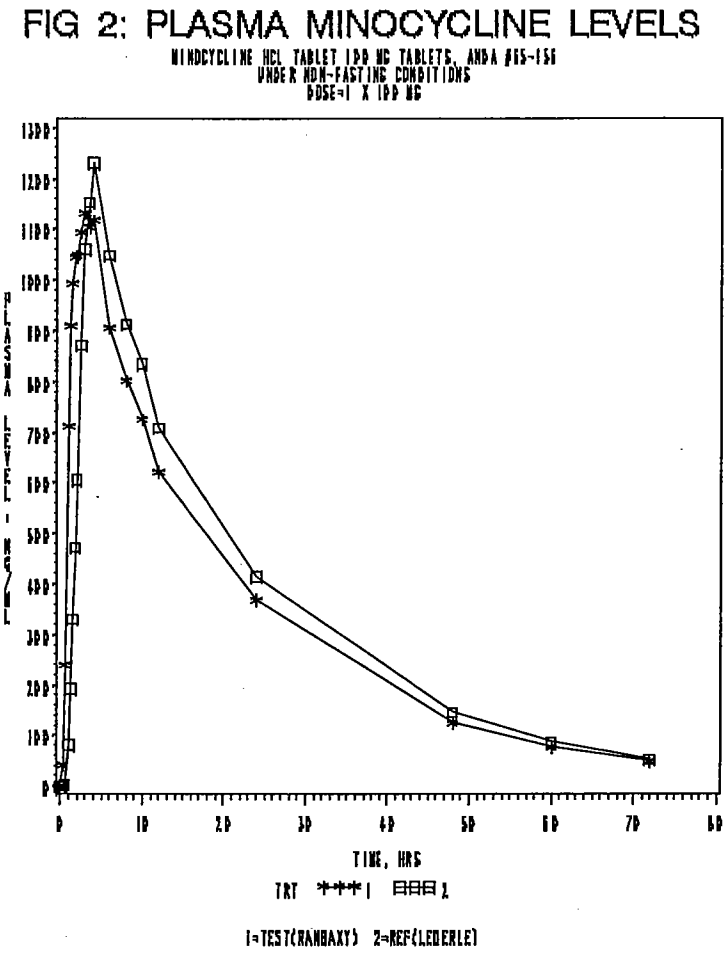
- ke and $AUC_{\infty}$ were determined for all subjects. If there are cases in which Ke cannot be calculated, indicate if you agree or disagree with firm's decision. N/A
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as $T_{max}$: None
  c. first measurable drug concentration as $C_{max}$: none
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? If so, did these affect the integrity of the study? There was significant sequence effect (p=0.03) for LNAUCT and LNAUCI. However, this is a single-dose study conducted in normal subjects, minocycline is not an endogenous entity, adequate washout period had been allowed, and the study meets all scientific and statistic criteria, therefore the significant sequence effect should not affect the integrity of the study.
- Are the 90% confidence intervals for $AUC_{0-t}$, $AUC_{\infty}$, Cmax within the acceptable limits of 80-125%. Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect The study was conducted in 1 group only.

**Conclusion:** The single-dose fed bioequivalence study is acceptable.

**Table 20 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study**

| | TEST MEAN | SD | REF. MEAN | SD | TEST/REF. |
|---|---|---|---|---|---|
| TIME HR | | | | | |
| 0 | 0.000 | 0.000 | 0.000 | 0.000 | . |
| 0.25 | 40.721 | 84.747 | 0.000 | 0.000 | . |
| 0.5 | 239.125 | 250.815 | 2.813 | 13.778 | 85.022 |
| 1 | 709.996 | 388.050 | 80.542 | 69.697 | 8.815 |
| 1.25 | 909.804 | 422.553 | 192.904 | 145.641 | 4.716 |
| 1.5 | 992.125 | 402.366 | 330.079 | 233.592 | 3.006 |
| 1.75 | 1046.708 | 340.025 | 471.396 | 274.653 | 2.220 |
| 2 | 1047.083 | 294.389 | 606.542 | 321.571 | 1.726 |
| 2.5 | 1093.583 | 240.069 | 870.875 | 329.658 | 1.256 |
| 3 | 1132.500 | 223.556 | 1061.375 | 316.139 | 1.067 |
| 3.5 | 1105.125 | 199.578 | 1152.500 | 217.619 | 0.959 |
| 4 | 1118.083 | 194.017 | 1231.042 | 230.424 | 0.908 |
| 6 | 906.917 | 172.681 | 1048.792 | 226.002 | 0.865 |
| 8 | 802.875 | 133.931 | 912.750 | 199.545 | 0.880 |
| 10 | 725.542 | 120.057 | 835.833 | 175.555 | 0.868 |
| 12 | 622.417 | 116.968 | 708.667 | 150.049 | 0.878 |
| 24 | 369.125 | 78.884 | 415.292 | 91.226 | 0.889 |
| 48 | 125.038 | 35.172 | 145.842 | 46.649 | 0.857 |
| 60 | 75.325 | 26.214 | 86.633 | 33.998 | 0.869 |
| 72 | 49.158 | 20.382 | 52.146 | 22.969 | 0.943 |

**Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study**

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## B. Formulation Data

| | 50 mg | | 75 mg | | 100 mg | |
|---|---|---|---|---|---|---|
| Ingredients | mg | % | mg | % | mg | % |
| Minocycline Hydrochloride USP * equivalent to Minocycline | (50) | 30.000 | (75) | 30.000 | (100) | 30.000 |
| Crospovidone, NF | | | | | | |
| Colloidal Silicon Dioxide, NF | | | | | | |
| Silicified Microcrystalline Cellulose | | | | | | |
| Lactose Monohydrate** NF | | | | | | |
| Stearic Acid, NF | | | | | | |
| Magnesium Stearate, NF | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| Tablet Weight | 185.40 | | 278.10 | | 370.80 | |

*,** The quantity of these ingredients may need to be adjusted based on the % w/w assay of the active ingredient, Minocycline Hydrochloride in order to maintain constant core tablet weight.

***

#

**contains the following ingredients:**

Hypromellose,
Titanium Dioxide,
Polyethylene Glycol 6000,
Iron Oxide Yellow,

**Note:** Each Minocycline Hydrochloride Tablet, USP 100mg contains of iron. With respect to the maximum recommended dose of 300mg/day, the maximum iron content per day for the 100mg strength is which is less than the permitted limit of 5 mg iron per day as cited in 21 CFR 73.1200 (c)

## C. Dissolution Data

**Table 1**

| Sampling Time (min.) | Test Product: Minocycline HCl Tablet Strength: 50 mg Lot No.: 73380202 | | | Reference Product: Minocin Capsule Strength: 50 mg Lot No. : 3023755 | | |
|---|---|---|---|---|---|---|
| | Mean % | %CV | Range (%) | Mean % | %CV | Range (%) |
| 10 | 101 | 1.36 | [redacted] | 31 | 8.06 | [redacted] |
| 20 | 101 | 1.15 | | 52 | 12.68 | |
| 30 | 101 | 0.95 | | 63 | 9.18 | |
| 45 | 102 | 1.27 | | 80 | 8.01 | |
| Date of analysis | 09/26/2002 | | | 01/21/2003 | | |
| **Sampling Time (min.)** | **Test Product: Minocycline HCl Tablet Strength: 75 mg Lot No.: 73380201** | | | **Reference Product: Dynacin Capsule Strength: 75 mg Lot No. : 1F02041** | | |
| | Mean % | %CV | Range (%) | Mean % | %CV | Range (%) |
| 10 | 102 | 1.14 | [redacted] | 75 | 16.64 | [redacted] |
| 20 | 102 | 1.13 | | 96 | 1.37 | |
| 30 | 102 | 1.13 | | 98 | 1.43 | |
| 45 | 102 | 1.21 | | 99 | 1.42 | |
| Date of analysis | 09/26/2002 | | | 01/21/2003 | | |
| **Sampling Time (min.)** | **Test Product: Minocycline HCl Tablet Strength: 100 mg Lot No.: 73400201** | | | **Reference Product: Minocin Capsule Strength: 100 mg Lot No. : 3013510** | | |
| | Mean % | %CV | Range (%) | Mean % | %CV | Range (%) |
| 10 | 103 | 1.31 | [redacted] | 30 | 9.45 | [redacted] |
| 20 | 104 | 1.24 | | 48 | 8.04 | |
| 30 | 104 | 1.12 | | 60 | 4.61 | |
| 45 | 104 | 1.17 | | 74 | 3.78 | |
| Date of analysis | 9/24/2002 | | | 1/17/2002 & 1/18/2003 | | |

The firm, however, needs to repeat the dissolution testing comparing its test products with the current RLD, Medicis' minocyline tablets, 50 mg, 75 mg and 100 mg.

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**D. Consult Reviews**

None

## E. SAS Output

# Fasting Study

The GLM Procedure

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SUB | 28 | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 |
| TRT | 2 | 1 2 |
| PER | 2 | 1 2 |
| SEQ | 2 | 1 2 |

Number of observations 56

Dependent Variable: LAUCT

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 29 | 4.73255619 | 0.16319159 | 16.95 | <.0001 |
| Error | 26 | 0.25037741 | 0.00962990 | | |
| Corrected Total | 55 | 4.98293360 | | | |

| R-Square | Coeff Var | Root MSE | LAUCT Mean |
|---|---|---|---|
| 0.949753 | 0.957381 | 0.098132 | 10.25006 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.00050540 | 0.00050540 | 0.05 | 0.8206 |
| SUB(SEQ) | 26 | 4.67887747 | 0.17995683 | 18.69 | <.0001 |
| PER | 1 | 0.00945719 | 0.00945719 | 0.98 | 0.3308 |
| TRT | 1 | 0.04371612 | 0.04371612 | 4.54 | 0.0427 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.00050540 | 0.00050540 | 0.05 | 0.8206 |
| SUB(SEQ) | 26 | 4.67887747 | 0.17995683 | 18.69 | <.0001 |
| PER | 1 | 0.00945719 | 0.00945719 | 0.98 | 0.3308 |
| TRT | 1 | 0.04371612 | 0.04371612 | 4.54 | 0.0427 |

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.00050540 | 0.00050540 | 0.00 | 0.9581 |

Standard

| Parameter | Estimate | Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| TRT&I VS TRT&K | 0.05588005 | 0.02622690 | 2.13 | 0.0427 |

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The GLM Procedure

Dependent Variable: LAUCI

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 29 | 5.17959902 | 0.17860686 | 19.74 | <.0001 |
| Error | 26 | 0.23520379 | 0.00904630 | | |
| Corrected Total | 55 | 5.41480282 | | | |

| R-Square | Coeff Var | Root MSE | LAUCI Mean |
|---|---|---|---|
| 0.956563 | 0.923253 | 0.095112 | 10.30184 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.00052941 | 0.00052941 | 0.06 | 0.8107 |
| SUB(SEQ) | 26 | 5.13111549 | 0.19735060 | 21.82 | <.0001 |
| PER | 1 | 0.00864518 | 0.00864518 | 0.96 | 0.3373 |
| TRT | 1 | 0.03930895 | 0.03930895 | 4.35 | 0.0471 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.00052941 | 0.00052941 | 0.06 | 0.8107 |
| SUB(SEQ) | 26 | 5.13111549 | 0.19735060 | 21.82 | <.0001 |
| PER | 1 | 0.00864518 | 0.00864518 | 0.96 | 0.3373 |
| TRT | 1 | 0.03930895 | 0.03930895 | 4.35 | 0.0471 |

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.00052941 | 0.00052941 | 0.00 | 0.9591 |

| Parameter | Estimate | Standard Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| TRT&I VS TRT&K | 0.05298851 | 0.02541976 | 2.08 | 0.0471 |

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The GLM Procedure

Dependent Variable: LCMAX

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 29 | 5.13602796 | 0.17710441 | 9.38 | <.0001 |
| Error | 26 | 0.49112070 | 0.01888926 | | |

| | | |
|---|---|---|
| Corrected Total | 55 | 5.62714865 |

| R-Square | Coeff Var | Root MSE | LCMAX Mean |
|---|---|---|---|
| 0.912723 | 1.862945 | 0.137438 | 7.377470 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.02955648 | 0.02955648 | 1.56 | 0.2221 |
| SUB(SEQ) | 26 | 4.92151772 | 0.18928914 | 10.02 | <.0001 |
| PER | 1 | 0.00496291 | 0.00496291 | 0.26 | 0.6126 |
| TRT | 1 | 0.17999083 | 0.17999083 | 9.53 | 0.0048 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.02955648 | 0.02955648 | 1.56 | 0.2221 |
| SUB(SEQ) | 26 | 4.92151772 | 0.18928914 | 10.02 | <.0001 |
| PER | 1 | 0.00496291 | 0.00496291 | 0.26 | 0.6126 |
| TRT | 1 | 0.17999083 | 0.17999083 | 9.53 | 0.0048 |

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term

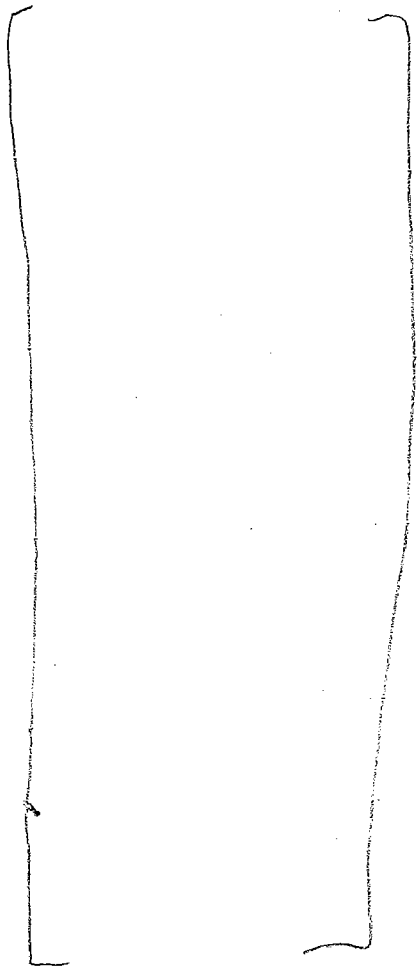
| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.02955648 | 0.02955648 | 0.16 | 0.6960 |

| Parameter | Estimate | Standard Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| TRT&I VS TRT&K | 0.11338645 | 0.03673190 | 3.09 | 0.0048 |

RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS *

| Obs | SUB | PER | SEQ | TRT | AUCTO_N | AUCIO_N | CMAXO_N | TMAXO_N |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 1 | 1 | | | | |
| 2 | 2 | 2 | 2 | 1 | | | | |
| 3 | 3 | 1 | 1 | 1 | | | | |
| 4 | 4 | 2 | 2 | 1 | | | | |
| 5 | 5 | 1 | 1 | 1 | | | | |
| 6 | 6 | 1 | 1 | 1 | | | | |
| 7 | 7 | 1 | 1 | 1 | | | | |
| 8 | 8 | 2 | 2 | 1 | | | | |
| 9 | 9 | 1 | 1 | 1 | | | | |
| 10 | 10 | 2 | 2 | 1 | | | | |
| 11 | 11 | 2 | 2 | 1 | | | | |
| 12 | 12 | 1 | 1 | 1 | | | | |
| 13 | 13 | 2 | 2 | 1 | | | | |
| 14 | 14 | 2 | 2 | 1 | | | | |
| 15 | 15 | 1 | 1 | 1 | | | | |
| 16 | 16 | 2 | 2 | 1 | | | | |
| 17 | 17 | 2 | 2 | 1 | | | | |
| 18 | 18 | 2 | 2 | 1 | | | | |
| 19 | 19 | 2 | 2 | 1 | | | | |

| | | | | |
|---|---|---|---|---|
| 20 | 20 | 1 | 1 | 1 |
| 21 | 21 | 1 | 1 | 1 |
| 22 | 22 | 2 | 2 | 1 |
| 23 | 23 | 1 | 1 | 1 |
| 24 | 24 | 2 | 2 | 1 |
| 25 | 25 | 1 | 1 | 1 |
| 26 | 26 | 2 | 2 | 1 |
| 27 | 27 | 1 | 1 | 1 |
| 28 | 28 | 1 | 1 | 1 |
| 29 | 1 | 2 | 1 | 2 |
| 30 | 2 | 1 | 2 | 2 |
| 31 | 3 | 2 | 1 | 2 |
| 32 | 4 | 1 | 2 | 2 |
| 33 | 5 | 2 | 1 | 2 |
| 34 | 6 | 2 | 1 | 2 |
| 35 | 7 | 2 | 1 | 2 |
| 36 | 8 | 1 | 2 | 2 |
| 37 | 9 | 2 | 1 | 2 |
| 38 | 10 | 1 | 2 | 2 |
| 39 | 11 | 1 | 2 | 2 |
| 40 | 12 | 2 | 1 | 2 |
| 41 | 13 | 1 | 2 | 2 |
| 42 | 14 | 1 | 2 | 2 |
| 43 | 15 | 2 | 1 | 2 |
| 44 | 16 | 1 | 2 | 2 |
| 45 | 17 | 1 | 2 | 2 |
| 46 | 18 | 1 | 2 | 2 |
| 47 | 19 | 1 | 2 | 2 |
| 48 | 20 | 2 | 1 | 2 |
| 49 | 21 | 2 | 1 | 2 |
| 50 | 22 | 1 | 2 | 2 |
| 51 | 23 | 2 | 1 | 2 |
| 52 | 24 | 1 | 2 | 2 |
| 53 | 25 | 2 | 1 | 2 |
| 54 | 26 | 1 | 2 | 2 |
| 55 | 27 | 2 | 1 | 2 |
| 56 | 28 | 2 | 1 | 2 |



* = Reason for same Cmax but different Tmax was because there were 2 time points both with the same concentration, therefore both time points are qualified for Tmax. The firm must have picked a different one from the one the reviewer picked.

## NON-FASTING STUDY

The GLM Procedure

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SUB | 24 | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 |
| TRT | 2 | 1 2 |
| PER | 2 | 1 2 |
| SEQ | 2 | 1 2 |

Number of observations 48

Dependent Variable: LAUCT

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 25 | 1.61609186 | 0.06464367 | 17.38 | <.0001 |
| Error | 22 | 0.08182812 | 0.00371946 | | |
| Corrected Total | 47 | 1.69791999 | | | |

| R-Square | Coeff Var | Root MSE | LAUCT Mean |
|---|---|---|---|
| 0.951807 | 0.603930 | 0.060987 | 10.09842 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.29112074 | 0.29112074 | 78.27 | <.0001 |
| SUB(SEQ) | 22 | 1.26765844 | 0.05762084 | 15.49 | <.0001 |
| PER | 1 | 0.00312751 | 0.00312751 | 0.84 | 0.3691 |
| TRT | 1 | 0.05418517 | 0.05418517 | 14.57 | 0.0009 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.29112074 | 0.29112074 | 78.27 | <.0001 |
| SUB(SEQ) | 22 | 1.26765844 | 0.05762084 | 15.49 | <.0001 |
| PER | 1 | 0.00312751 | 0.00312751 | 0.84 | 0.3691 |
| TRT | 1 | 0.05418517 | 0.05418517 | 14.57 | 0.0009 |

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.29112074 | 0.29112074 | 5.05 | 0.0349 |

| Parameter | Estimate | Standard Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| TRT&I VS TRT&K | -0.06719695 | 0.01760554 | -3.82 | 0.0009 |

Dependent Variable: LAUCI

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 25 | 1.68256747 | 0.06730270 | 15.91 | <.0001 |
| Error | 22 | 0.09308547 | 0.00423116 | | |
| Corrected Total | 47 | 1.77565294 | | | |

| R-Square | Coeff Var | Root MSE | LAUCI Mean |
|---|---|---|---|
| 0.947577 | 0.641148 | 0.065047 | 10.14545 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.30280085 | 0.30280085 | 71.56 | <.0001 |
| SUB(SEQ) | 22 | 1.32151472 | 0.06006885 | 14.20 | <.0001 |
| PER | 1 | 0.00450778 | 0.00450778 | 1.07 | 0.3132 |
| TRT | 1 | 0.05374411 | 0.05374411 | 12.70 | 0.0017 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.30280085 | 0.30280085 | 71.56 | <.0001 |
| SUB(SEQ) | 22 | 1.32151472 | 0.06006885 | 14.20 | <.0001 |
| PER | 1 | 0.00450778 | 0.00450778 | 1.07 | 0.3132 |
| TRT | 1 | 0.05374411 | 0.05374411 | 12.70 | 0.0017 |

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.30280085 | 0.30280085 | 5.04 | 0.0351 |

| Parameter | Estimate | Standard Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| TRT&I VS TRT&K | -0.06692291 | 0.01877755 | -3.56 | 0.0017 |



The GLM Procedure

Dependent Variable: LCMAX

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 25 | 1.08128144 | 0.04325126 | 8.44 | <.0001 |
| Error | 22 | 0.11274774 | 0.00512490 | | |
| Corrected Total | 47 | 1.19402918 | | | |

| R-Square | Coeff Var | Root MSE | LCMAX Mean |
|---|---|---|---|
| 0.905574 | 0.998749 | 0.071588 | 7.167805 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.03528320 | 0.03528320 | 6.88 | 0.0155 |
| SUB(SEQ) | 22 | 1.04586337 | 0.04753924 | 9.28 | <.0001 |
| PER | 1 | 0.00000087 | 0.00000087 | 0.00 | 0.9897 |
| TRT | 1 | 0.00013401 | 0.00013401 | 0.03 | 0.8730 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.03528320 | 0.03528320 | 6.88 | 0.0155 |
| SUB(SEQ) | 22 | 1.04586337 | 0.04753924 | 9.28 | <.0001 |
| PER | 1 | 0.00000087 | 0.00000087 | 0.00 | 0.9897 |
| TRT | 1 | 0.00013401 | 0.00013401 | 0.03 | 0.8730 |

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 1 | 0.03528320 | 0.03528320 | 0.74 | 0.3983 |

## F. Additional Attachments

None

BIOEQUIVALENCY DEFICIENCIES

ANDA: #65-156 APPLICANT: Ranbaxy Laboratories

DRUG PRODUCT: Minocycline Hydrochloride Tablets USP,
50 mg, 75 mg, 100 mg

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

1. Please conduct dissolution testing for all three strengths comparing your test products with the current Reference Listed Drug (Medicis' Minocycline Tablets, 50 mg, 75 mg and 100 mg) in 900 mL of water using USP Apparatus II (paddle) at 50 rpm. If appropriate, please calculate F2 metrics comparing lower strengths to the highest strength and the test to the reference for each strength.

2. Please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

3. Also, for future submissions the selected ——— ——— for inclusion should be serially selected as recommended in the Guidance for Industry Bioanalytical Method Validation issued in May 2001.

Sincerely yours,

Barbara M. Davit

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

CC: ANDA #65-156
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-652/L. Chuang LWC 10/15/2003
HFD-652/Y. Huang YH 10/15/2003
HFD-617/A. Sigler
for HFD-650/Dale Conner BNC 10.15.03

BIOEQUIVALENCY - ACCEPTABLE (Dissolution Incomplete) submission date: 2/10/2003

1. FASTING STUDY (STF) 01C Strengths: 100 mg
Clinical:
Analytical:

**Outcome: AC**

2. **FOOD STUDY** (STP) 01C Strengths: 100 mg
Clinical:
Analytical:

**Outcome: AC**

3. **DISSOLUTION WAIVER** (DIW) 01C Strength: 50 mg
**Outcome: IC**

4. **DISSOLUTION WAIVER** (DIW) 01C Strength: 75 mg
**Outcome: IC**

Outcome Decisions: **AC** - Acceptable
**IC** - Incomplete

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: #65-156 APPLICANT: Ranbaxy Laboratories

DRUG PRODUCT: Minocycline Hydrochloride Tablets USP,
50 mg, 75 mg, 100 mg

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

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in the USP.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M Davis

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

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 65-156 |
| **Drug Product Name** | Minocycline Hydrochloride Tablets USP |
| **Strength** | 50 mg, 75 mg, 100 mg |
| **Applicant Name** | Ranbaxy Pharmaceuticals Inc. |
| **Address** | 600 College Road East, Princeton, New Jersey 08540 |
| **Submission Date(s)** | February 10, 2003 (Original Submission) |
| **Amendment Date(s)** | November 3, 2003 (Current amendment) |
| **Reviewer** | Lin-Whei Chuang |
| **First Generic** | No |
| **File Location** | V:\FIRMSNZ\RANBAXY\LTRS&REV\65156A1103.doc |

## Executive Summary

This application for minocycline hydrochloride tablets references Minocin® Capsules of Wyeth Pharms Inc. in the in vivo BE studies and Dynacin® Tablets of Medicis in the in vitro dissolution tests. This is because currently the RLD for minocycline hydrochloride tablets is Medicis' Dynacin® Tablets (since 4/2003), but at the time of this submission (2/10/2003) there was no reference listed drug for minocycline hydrochloride tablet in the Orange Book. The FDA subsequently determined that the withdrawal of Minocin® tablet from sale was not due to safety or efficacy reasons.

Both fasting and fed BE studies using Minocin® capsules 100 mg as the RLD were found acceptable in the review of 10/15/2003. The test formulations of the 50 mg, 75 mg, and 100 mg tablets are proportionally similar. The waiver request of in vivo BE requirements for the 50 mg and 75 mg tablets is pending because the firm had conducted in vitro dissolution (900 mL of water, paddle at 50 rpm) testing against Minocin® capsules and DBE requested the in vitro dissolution testing to be conducted against Dynacin® tablets as shown below in the 3 deficiencies sent to the firm on 10/21/2003:

1. *Please conduct dissolution testing for all three strengths comparing your test products with the current Reference Listed Drug (Medicis' Minocycline Tablets, 50 mg, 75 mg and 100 mg) in 900 mL of water using USP Apparatus II (paddle) at 50 rpm. If appropriate, please calculate F2 metrics comparing lower strengths to the highest strength and the test to the reference for each strength.*

2. *Please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.*

3. *Also, for future submissions the selected [redacted] for inclusion should be serially selected as recommended in the Guidance for Industry Bioanalytical Method Validation issued in May 2001.*

The firm has responded to all 3 deficiencies satisfactorily and the application is acceptable.

**Review:**

1. Firm's Response to Deficiency #1:

The firm has conducted comparative dissolution testing on all 3 strengths of the test products and the 75 mg and 100 mg strengths of Medicis' Dynacin® tablets as shown in Table 1 below. The Medicis' 50 mg tablets are not available in the market and therefore were not tested.

**Table 1: Dissolution Testing (USP Method: 900 mL of water, paddle at 50 rpm)**

| Sampling Time (min.) | Test Product: Minocycline HCl Tablet Strength: 50 mg Lot No.: 73380202 | | | Reference Product: Dynacin® Tablets (Minocycline Tablet of Medici , Not Available in the Market) Strength: 50 mg Lot No: N/A | | |
|---|---|---|---|---|---|---|
| | Mean % | %CV | Range (%) | Mean % | %CV | Range (%) |
| 10 | 101 | 1.36 | | N/A | | |
| 20 | 101 | 1.15 | | | | |
| 30 | 101 | 0.95 | | | | |
| 45 | 102 | 1.27 | | | | |
| Date of analysis | 09/26/2002 | | | | | |
| Sampling Time (min.) | Test Product: Minocycline HCl Tablet Strength: 75 mg Lot No.: 73390201 | | | Reference Product: Dynacin® Tablets (Minocycline Tablet of Medici) Strength: 75 mg Lot No. : 038621 | | |
| | Mean % | %CV | Range (%) | Mean % | %CV | Range (%) |
| 10 | 102 | 1.14 | | 25 | 22.67 | |
| 20 | 102 | 1.13 | | 59 | 16.14 | |
| 30 | 102 | 1.13 | | 85 | 9.05 | |
| 45 | 102 | 1.21 | | 94 | 3.92 | |
| Date of analysis | 09/25/20 | | | 10/29/2003 | | |
| Sampling Time (min.) | Test Product: Minocycline HCl Tablet Strength: 100 mg Lot No.: 73400201 | | | Reference Product: Dynacin® Tablets (Minocycline Tablet of Medici ) Strength: 100 mg Lot No. : 037673 | | |
| | Mean % | %CV | Range (%) | Mean % | %CV | Range (%) |
| 10 | 103 | 1.31 | | 21 | 19.78 | |
| 20 | 104 | 1.24 | | 51 | 4.65 | |
| 30 | 104 | 1.12 | | 81 | 9.59 | |
| 45 | 104 | 1.17 | | 100 | 2.88 | |
| Date of analysis | 9/24/2002 | | | 10/28/2003 | | |

APPEARS THIS WAY ON ORIGINAL

Reviewer's Comments:

a. All 3 strengths of the test product are fast-dissolving ( o in 10 min.) and therefore no F2 factors were calculated.

b. The mean % dissolved for 2 of the 4 sampling time points of Dynacin® 75 mg tablet and 1 out of the 4 sampling time points of Dynacin 100 mg tablet had high CV ( >16%) , therefore F2 calculation was not conducted between the 2 reference strengths.

c. Both the test product and the available reference product comply with the USP dissolution specification of "NLT 75% (Q) in 45 min.". The comparative dissolution data submitted by the firm are acceptable.

2. Firm's Response to Deficiency #2:
The address of the laboratory conducting the dissolution testing is provided below:

Ohm Laboratories, Inc.
PO Box 7397
1385 Livingston Avenue
North Brunswick, NJ 08902

Reviewer's Comment:
The firm's response is acceptable.

3. Firm's Response to Deficiency #3:
The firm has noted and acknowledged the Agency's comment.

Reviewer's Comment:
The firm's response is acceptable.

**Overall Comments:**
1. The firm's responses submitted in this amendment are acceptable.
2. Both fasting and fed BE studies are acceptable as previously reviewed on 10/15/2003.
3. The comparative dissolution conducted by the firm using the USP method is acceptable.
4. The test formulations of the 50 mg, 75 mg, and 100 mg tablets are proportionally similar as shown in the review of 10/15/2003. The waiver request of in vivo BE requirements for the 50 mg and 75 mg tablets is granted per 21 CFR Section 320.22(d)(2).

**Recommendations:**

1. The fasting and non-fasting bioequivalence studies conducted by Ranbaxy Pharmaceuticals Inc. on its minocycline hydrochloride 100 mg tablets, lot #73400201, comparing it to Minocin 100 mg capsule, lot #3013510, have been found acceptable previously by the Division of Bioequivalence.
2. The comparative dissolution tests conducted by Ranbaxy Pharmaceuticals Inc. on its minocycline hydrochloride 50 mg, 75 mg and 100 mg tablets, comparing them to Dynacin 75 mg and 100 mg tablets using USP apparatus II (paddle) at 50 rpm in 900 mL of water have been found acceptable by the Division of Bioequivalence.

3. The formulations of Ranbaxy's minocycline 50 mg and 75 mg tablets are proportionally similar to the 100 mg tablet which underwent *in vivo* bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 50 mg and 75 mg tablets is granted per 21 CFR 320.22(d)(2).

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of water using USP Apparatus II (paddle) at 50 rpm. The test products should meet the following Agency-recommended (USP) specification:

   Not less than 75% (Q) of the labeled amount of minocycline hydrochloride in the dosage form is dissolved in 45 minutes.

Lin-Whei Chuang 12/12/03

Lin-Whei Chuang, Branch 1, Date signed

12/12/2003

Yih-Chain Huang, Ph.D., Team Leader, Branch 1, Date signed

Barbara M Davit 12/12/03

for

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: #65-156 APPLICANT: Ranbaxy Laboratories

DRUG PRODUCT: Minocycline Hydrochloride Tablets USP,
50 mg, 75 mg, 100 mg

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

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in the USP.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M. Davit

for

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

CC: ANDA #65-156
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ L. Chuang

Endorsements: (Final with Dates)
HFD-652/ L. Chuang LWC 12/12/03
HFD-652/ Y. Huang Y-H 12/12/2003
HFD-617/ A. Sigler
HFD-650/ D. Conner BWD 12/12/03

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BIOEQUIVALENCY - ACCEPTABLE submission date: 11/3/2003

1. **STUDY AMENDMENT** (STA) o/c
**Dissolution Data**

Strengths: 50 mg, 75 mg, & 100 mg
**Outcome: AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

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

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**ANDA # : 65-156** SPONSOR : Ranbaxy Pharmaceuticals

**DRUG AND DOSAGE FORM :** **Minocycline Hydrochloride Tablets USP**
**STRENGTHS :** 50 mg, 75 mg and 100 mg
**TYPES OF STUDIES :** Fasting and Non-Fasting *In Vivo* BE Studies on the 100 mg strength; Dissolution Tests on all strengths; and Waiver Requests on the 50 mg and 75 mg strengths.

**CLINICAL SITE:** [redacted]
**ANALYTICAL SITE:** : [redacted]

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STUDY SUMMARY : Both studies are acceptable
DISSOLUTION : Acceptable with Agency recommended specifications.
WAIVER REQUEST: Granted per 21 CFR 320.22(d)(2)

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**DSI INSPECTION STATUS**

| Inspection needed: NO | Inspection status: | Inspection results: |
|---|---|---|
| First Generic _No_<br>New facility No<br>For cause _____<br>Other _____ | Inspection requested: (date)<br>Inspection completed: (date) | |

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PRIMARY REVIEWER : Lin-Whei Chuang BRANCH : I

INITIAL : LWC DATE : 12/12/03

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TEAM LEADER : Yih-Chain Huang, Ph.D. BRANCH : I

INITIAL : [signature] DATE : 12/12/2003

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for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : Barbara M. Davit DATE : 12/12/03

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 65-156 |
| **Drug Product Name** | Minocycline Hydrochloride Tablets USP |
| **Strength** | 50 mg, 75 mg, 100 mg |
| **Applicant Name** | Ranbaxy Pharmaceuticals Inc. |
| **Address** | 600 College Road East, Princeton, New Jersey 08540 |
| **Submission Date(s)** | February 10, 2003 (Original Submission) |
| **Amendment Date(s)** | November 3, 2003 (Current amendment) |
| **Reviewer** | Lin-Whei Chuang |
| **First Generic** | No |
| **File Location** | V:\FIRMSNZ\RANBAXY\LTRS&REV\65156A1103.doc |

## Executive Summary

This application for minocycline hydrochloride tablets references Minocin® Capsules of Wyeth Pharms Inc. in the in vivo BE studies and Dynacin® Tablets of Medicis in the in vitro dissolution tests. This is because currently the RLD for minocycline hydrochloride tablets is Medicis' Dynacin® Tablets (since 4/2003), but at the time of this submission (2/10/2003) there was no reference listed drug for minocycline hydrochloride tablet in the Orange Book. The FDA subsequently determined that the withdrawal of Minocin® tablet from sale was not due to safety or efficacy reasons.

Both fasting and fed BE studies using Minocin® capsules 100 mg as the RLD were found acceptable in the review of 10/15/2003. The test formulations of the 50 mg, 75 mg, and 100 mg tablets are proportionally similar. The waiver request of in vivo BE requirements for the 50 mg and 75 mg tablets is pending because the firm had conducted in vitro dissolution (900 mL of water, paddle at 50 rpm) testing against Minocin® capsules and DBE requested the in vitro dissolution testing to be conducted against Dynacin® tablets as shown below in the 3 deficiencies sent to the firm on 10/21/2003:

1. *Please conduct dissolution testing for all three strengths comparing your test products with the current Reference Listed Drug (Medicis' Minocycline Tablets, 50 mg, 75 mg and 100 mg) in 900 mL of water using USP Apparatus II (paddle) at 50 rpm. If appropriate, please calculate F2 metrics comparing lower strengths to the highest strength and the test to the reference for each strength.*

2. *Please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.*

3. *Also, for future submissions the selected [redacted] for inclusion should be serially selected as recommended in the Guidance for Industry Bioanalytical Method Validation issued in May 2001.*

The firm has responded to all 3 deficiencies satisfactorily and the application is acceptable.

**Review:**

1. Firm's Response to Deficiency #1:

The firm has conducted comparative dissolution testing on all 3 strengths of the test products and the 75 mg and 100 mg strengths of Medicis' Dynacin® tablets as shown in Table 1 below. The Medicis' 50 mg tablets are not available in the market and therefore were not tested.

**Table 1: Dissolution Testing (USP Method: 900 mL of water, paddle at 50 rpm)**

| Sampling Time (min.) | Test Product: Minocycline HCl Tablet Strength: 50 mg Lot No.: 73380202 | | | Reference Product: Dynacin® Tablets (Minocycline Tablet of Medici , Not Available in the Market) Strength: 50 mg Lot No: N/A | | |
|---|---|---|---|---|---|---|
| | Mean % | %CV | Range (%) | Mean % | %CV | Range (%) |
| 10 | 101 | 1.36 | [redacted] | N/A | | |
| 20 | 101 | 1.15 | | | | |
| 30 | 101 | 0.95 | | | | |
| 45 | 102 | 1.27 | | | | |
| Date of analysis | 09/26/2002 | | | | | |

APPEARS THIS WAY ON ORIGINAL

| Sampling Time (min.) | Test Product: Minocycline HCl Tablet Strength: 75 mg Lot No.: 73390201 | | | Reference Product: Dynacin® Tablets (Minocycline Tablet of Medici) Strength: 75 mg Lot No. : 038621 | | |
|---|---|---|---|---|---|---|
| | Mean % | %CV | Range (%) | Mean % | %CV | Range (%) |
| 10 | 102 | 1.14 | [redacted] | 25 | 22.67 | [redacted] |
| 20 | 102 | 1.13 | | 59 | 16.14 | |
| 30 | 102 | 1.13 | | 85 | 9.05 | |
| 45 | 102 | 1.21 | | 94 | 3.92 | |
| Date of analysis | 09/25/2002 | | | 10/29/2003 | | |

| Sampling Time (min.) | Test Product: Minocycline HCl Tablet Strength: 100 mg Lot No.: 73400201 | | | Reference Product: Dynacin® Tablets (Minocycline Tablet of Medici ) Strength: 100 mg Lot No. : 037673 | | |
|---|---|---|---|---|---|---|
| | Mean % | %CV | Range (%) | Mean % | %CV | Range (%) |
| 10 | 103 | 1.31 | [redacted] | 21 | 19.78 | [redacted] |
| 20 | 104 | 1.24 | | 51 | 4.65 | |
| 30 | 104 | 1.12 | | 81 | 9.59 | |
| 45 | 104 | 1.17 | | 100 | 2.88 | |
| Date of analysis | 9/24/2002 | | | 10/28/2003 | | |

Reviewer's Comments:

a. All 3 strengths of the test product are fast-dissolving ( ≥ 85% in 10 min.) and therefore no F2 factors were calculated.

b. The mean % dissolved for 2 of the 4 sampling time points of Dynacin® 75 mg tablet and 1 out of the 4 sampling time points of Dynacin 100 mg tablet had high CV ( >16%) , therefore F2 calculation was not conducted between the 2 reference strengths.

c. Both the test product and the available reference product comply with the USP dissolution specification of "NLT 75% (Q) in 45 min.". The comparative dissolution data submitted by the firm are acceptable.

2. Firm's Response to Deficiency #2:
The address of the laboratory conducting the dissolution testing is provided below:

Ohm Laboratories, Inc.
PO Box 7397
1385 Livingston Avenue
North Brunswick, NJ 08902

Reviewer's Comment:
The firm's response is acceptable.

3. Firm's Response to Deficiency #3:
The firm has noted and acknowledged the Agency's comment.

Reviewer's Comment:
The firm's response is acceptable.

**Overall Comments:**
1. The firm's responses submitted in this amendment are acceptable.
2. Both fasting and fed BE studies are acceptable as previously reviewed on 10/15/2003.
3. The comparative dissolution conducted by the firm using the USP method is acceptable.
4. The test formulations of the 50 mg, 75 mg, and 100 mg tablets are proportionally similar as shown in the review of 10/15/2003. The waiver request of in vivo BE requirements for the 50 mg and 75 mg tablets is granted per 21 CFR Section 320.22(d)(2).

**Recommendations:**

1. The fasting and non-fasting bioequivalence studies conducted by Ranbaxy Pharmaceuticals Inc. on its minocycline hydrochloride 100 mg tablets, lot #73400201, comparing it to Minocin 100 mg capsule, lot #3013510, have been found acceptable previously by the Division of Bioequivalence.
2. The comparative dissolution tests conducted by Ranbaxy Pharmaceuticals Inc. on its minocycline hydrochloride 50 mg, 75 mg and 100 mg tablets, comparing them to Dynacin 75 mg and 100 mg tablets using USP apparatus II (paddle) at 50 rpm in 900 mL of water have been found acceptable by the Division of Bioequivalence.

3. The formulations of Ranbaxy's minocycline 50 mg and 75 mg tablets are proportionally similar to the 100 mg tablet which underwent *in vivo* bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 50 mg and 75 mg tablets is granted per 21 CFR 320.22(d)(2).

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of water using USP Apparatus II (paddle) at 50 rpm. The test products should meet the following Agency-recommended (USP) specification:

   Not less than 75% (Q) of the labeled amount of minocycline hydrochloride in the dosage form is dissolved in 45 minutes.

Lin-Whei Chuang 12/12/03

Lin-Whei Chuang, Branch 1, Date signed

12/12/2003

Yih-Chain Huang, Ph.D., Team Leader, Branch 1, Date signed

Barbara M Davit 12/12/03

for

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

APPEARS THIS WAY
ON ORIGINAL