

## WHO Public Inspection Report (WHOPIR) of a Contract Research Organization

The report is the property of the organization responsible for performing the inspection.

### Part 1: General information

Name of organization	Manipal AcuNova KH Clinical Research Centre
Physical address	4 <sup>th</sup> floor, Shirdi Sai Baba Cancer Hospital 576 104 Manipal, India
Postal address	Same as above
Telephone number	00 91 820 257 1201 / 2 2553
Fax number	00 91 820 257 1999
Summary of activities	Performance of clinical studies, including bioequivalence trials (clinical and bio-analytical parts)
<b>WHO reference number</b> Study	<b>HA 396</b> # 021 - 06 A randomized, open label, balanced, two treatment, two periods, two sequences, single dose, crossover bioequivalence study in 26 healthy human adult male subjects, under fasting condition with 21 days of washout period between doses.
Start and stop dates for each phase of the clinical study	Period 1 : 14 October 2006 to 18 October 2006 Period 2 : 04 November 2006 to 08 November 2006
Investigational Products	Nevirapine 200 mg Tablet Manufactured by : Matrix Laboratories Limited, F-4 & F-12, Malegaon, MIDC, Sinnar- 422 113, Nashik District, Maharashtra State, India. Batch number : A536003 Manufacturing date : July 2006
Reference Products	Viramune <sup>®</sup> (Nevirapine 200mg) Tablet Boehringer Ingelheim Pharmaceuticals Inc, USA Batch number : 558027A
<b>WHO reference number</b> Study	<b>HA 410</b> # 033-06 A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Tenofovir disoproxil fumarate 300 mg tablets (Matrix Laboratories Ltd, India) with Viread <sup>®</sup> (Tenofovir disoproxil fumarate) 300 mg tablets, manufactured for Gilead Sciences, Inc. USA, in 32 healthy human adult male subjects under fed conditions.

Start and stop dates for each phase of the clinical study	Period 1 : 20 January 2007 to 24 January 2007 Period 2 : 30 January 2007 to 3 February 2007
Investigational Products	Tenofovir disoproxil fumarate 300 mg Tablet Manufactured by: Matrix Laboratories Limited, F-4 & F-12, Malegaon, MIDC, Sinnar- 422 113, Nashik District, Maharashtra State, India. Batch number : T DFA536001 Manufacturing date: Nov. 2006.
Reference Products	Viread® (Tenofovir disoproxil fumarate 300 mg) Tablet Manufactured by Gilead Sciences, Foster city, CA 94404. Batch No: FDB023
Sponsor	Matrix Laboratories Limited, India
Date of inspection:	22 and 23 January 2008
Project (if any):	Prequalification Programme : Priority Essential Medicines

## Part 2: Summary

The purpose of the inspection was to assess the bioequivalence study performed at Manipal AcuNova KH Clinical Research Centre for the following products manufactured by Matrix Laboratories Limited:

**HA 396** : Nevirapine 200 mg Tablets,

**HA 410** : Tenofovir disoproxil fumarate 300 mg Tablet,

and to evaluate whether the clinical part of the bioequivalence study was conducted in compliance with the submitted and assessed protocol and Good Clinical Practices (GCP) and other relevant WHO or international Good Practices and standards where applicable.

Manipal AcuNova started its clinical and bio-analytical operations for bioavailability / bioequivalence studies, phase I studies and Clinical trials (phase II to phase IV) in August 2005 in Manipal and in July 2006 in Mangalore. There is a third facility of 60 beds in Bangalore still under construction without activity so far.

The Manipal AcuNova Clinical Pharmacology Unit located in Manipal is situated at the 4<sup>th</sup> floor of the Shirdi Sai Baba Cancer Hospital and is performing bio-analytical/bioavailability studies as well as phase I studies, clinical and bio-analytical parts.

The facilities for, reception, screening, consent and enrolment of the volunteers is located in the same hospital but on a different location on the ground floor.

There are a total of 24 beds in one ward and 6 beds in an ICU unit which can also be used as a Phase 1 ward.

This Prequalification Programme inspection was the first audit conducted by WHO at the Manipal site of Manipal AcuNova.



The site has been authorized by the Indian Regulatory Authority and was inspected in February 2005 and July 2006.

The site has also been previously inspected by the USFDA in September 2007.

## **Clinical**

Various areas of the clinical facilities were inspected including the 2 bedded facilities (24 beds and 6 beds), emergency room equipped for intensive care medical management, phlebotomy rooms, registration areas, screening areas, sample processing areas, pharmacy, washrooms and dining and recreation halls.

The facilities in the pharmacy consist of a humidity chamber for study drug storage. During the inspection, the remaining study drug samples were examined in the pharmacy.

Manipal AcuNova has a computerized data base where all of the volunteer are registered and identified with their photograph and the thumb print. The subject database is linked to biometric finger print identification software. Each Volunteer Data Sheet also contained a copy of the subject's identification document such as school leaving certificate, passport or driving licence.

A volunteer's consent for registration has to be obtained before he can be considered as a potential study subject. A separate consent is then administered for general screening for study eligibility. The consent documents were available in English, Hindi, and the local language Kannada.

A review of the qualification of the principal investigator who left the company was done as well as the qualification of Dr Srinivas Shenoy B, Clinical Pharmacologist, as well as one of the custodians and one of the phlebotomists, including the personal file, job description and training records.

The source data of the two studies including clinical data, bio-analytical data, laboratory reports, drug accountability records etc. and remaining study drug samples (when available) at the site were audited to verify the accuracy, consistency, completeness, and reliability of the study reports. The facilities for the clinical procedures and documentation for the studies were also reviewed. Various staff members were interviewed in relation to the conduct of the studies.

From the attendance sheet for pre-study meeting it appeared that the study personnel were informed of the study requirements and their roles.

There was a range of SOPs and associated records available and key SOPs and corresponding records were checked as the SOP for dispensing and dosing.

In the clinical facility, it appeared that the facilities and resources were adequate for support of the study workload.

Documentation of the clinical part of the studies included:

- Independent ethics committee review procedures
- Screening, and study consent forms



- Source data and results
- Master lists for subjects
- Documentation and SOPs relating to study drugs accountability and dispensing records, and study drug labels
- Randomization schedule
- Study drug administration
- Blood sample collection
- Lists of staff present during the study
- Master list of signatures of volunteers
- QA audit reports

### **Bio-analytical**

The laboratory is equipped with three LC-MS and two HPLC.

The source data, bio-analytical data, laboratory reports were audited to verify the accuracy, consistency, completeness, and reliability of the study reports. The facilities for bio-analytical procedures and documentation for the studies were also reviewed. Various staff members were interviewed in relation to the conduct of the studies.

Various documents were reviewed. This included method validation for Tenofovir and Nevirapine (analysed together), stock solution preparation, weighing, working standards and COA, source data, chromatograms (short term, long term, freeze thaw), validation and qualification. The concentrations indicated on chromatograms were checked against the reported tabulated data and dossier report.

Documentation of the bioanalytical part of the studies reviewed included for several subjects:

- Repeat analysis record
- Chromatograms for subjects for different periods
- Results of calibration curves, and quality controls were reviewed for all runs of the study

At the time of the inspection both studies were already accepted by the assessors.

### **Part 3: Conclusion**

Based on the people met and the documents reviewed, and considering the findings of the inspection, reflected in the observations listed in the inspection report, the studies inspected can be considered to have been conducted at an acceptable level of compliance with WHO Good Clinical Practices (GCP) and Good Laboratory Practices (GLP), by Manipal AcuNova KMC Clinical Pharmacology Unit located in Manipal, India.