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WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	HA596 Ondansetron Hydrochloride 8mg tablet
Study number	**Study #0211/006:**
Title of the study	A Randomized, Open-label, Two-treatment, Two-period, Two-sequence, Single dose, Two-way crossover bioequivalence study of Ondansetron Hydrochloride 8 mg tablet (containing Ondansetron Hydrochloride dehydrate eq. to Ondansetron 8mg) of Cadila Pharmaceuticals Ltd., India compared with Zofran 8mg tablets (containing Ondansetron Hydrochloride dehydrate eq. to Ondansetron 8mg) of GSK procured from Switzerland, in Healthy, adult, human subjects under fasting condition.
Clinical Part of the study: Name and address of the organization	**Cadila Pharmaceuticals Limited** 1389, Trasad Road, Dholka-387810 Ahmedabad, Gujarat, India Tel.: +91-2714-221481/83/84 Fax: +91-2714-221848
Bio-analytical laboratory: Name and address	**Cadila Pharmaceuticals Limited** 1389, Trasad Road, Dholka-387810 Ahmedabad, Gujarat, India Tel.: +91-2714-221481/83/84 Fax: +91-2714-221848
Date of inspection	16, 17, 18 and 19 December 2013

Part 2: Summary

The purpose of the inspection was to inspect the clinical and the bioanalytical part of the bioequivalence study performed at Cadila Pharmaceuticals Limited and to evaluate whether the study was conducted in compliance with the protocol, Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) where applicable.

General information about the site(s)

Cadila CRO was incorporated in the year 2002 as Pharmacology division of Cadila Pharmaceutical Limited. The facility has a built up area of about 11,155 sq. feet spread over three floors. The clinical facility has two separate clinics each housing 40 beds. The bioanalytical laboratory is located in same premises on the second floor, which has 5 triple quadrupole LC/MS systems; 2 API 4000, 1 API 3000 and 2 QPXE from Waters. The bioanalytical laboratory is also supported by other automated equipment.

History of WHO and/or regulatory agency inspections

This was the third WHO inspection of Cadila CRO. The CRO was previously inspected in 2005 and 2012. In addition, the CRO had been inspected by ANVISA in 2004, 2005, 2006 and 2009. EMA had inspected the CRO in 2013.

The DCGI have also inspected CRO in 2006, 2007, 2011 and 2013.

Focus of the inspection

The inspection focused on the bioequivalence study conducted for the product HA596 (Ondansetron 8mg tablet). The inspection covered most of the sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Inspected Areas

The inspection was started with an opening meeting. The company representatives introduced themselves. The inspector introduced himself and then he briefed the CRO about the PQ program and the purpose of the inspection. The Cadila CRO representatives informed the inspector that there had been some changes since the conduct of this study which included but not limited to online temperature monitoring system for deep freezers, freeze thaw cycles have been restricted to five for matrix lots used for method validation and project sample analysis, use of the Online Volunteer Information System (OVIS) and ECG recording procedure.

For first two days, inspectors focused to bioanalytical section and inspected following areas:

- Sample storage area housed several deep freezers which were connected with data loggers for continuous temperature monitoring
- Sample processing laboratory equipped with Solid Phase and Liquid-liquid extraction capabilities
- Balance room (three weighing balances with different capacities and uses), these balances were daily and quarterly calibrated/verified in-house and annually calibrated by outside vendor
- Working standard room (it is noted that working standards are prepared in-house by the formulation group)

- Micro Pipette calibration performed in-house at low, middle and high level with three month frequency
- LC-MS/MS instrument room
- Instruments used for sample analysis for HA596
- Tour of the laboratory
- Method development of Ondansetron performed. Several trials were taken to optimise various response and chromatographic conditions.
- Method development work was concluded
- SOP on method development dated 24/1/2011
- Sample traceability – transfer of samples from the clinical storage facility to the analytical laboratory storage prior to analysis. Relevant freezer accountability records were reviewed and temperature monitoring activities discussed.
- Solution preparation details (test and reference standard weights, CC and QC stock solutions, buffers and reagents). Associated balance logbooks and pipette calibration documentation also reviewed
  Review of pre-method validation which included several experiments such as matrix effect, specificity, recovery, precision & accuracy. It was however found that laboratory forgot to perform auto sampler stability and no evaluation of regression equation as required by the SOP on method development
- Method validation included system suitability, batch processing, auto injector carry over, specificity, screening of biological matrix, first day stability assessment, precision & accuracy batch
- Matrix effect using 7 different plasma
- Bench top stability at ambient temperature.
- Wet extract stability at 2-8ºC (15/4/2011)
- Auto sampler stability dated
- Freeze thaw stability for cycle I, II, III, IV and V at -20ºC and -70ºC
- Amendment to bioanalytical method validation report,
- Long term stability in matrix (LTM), amendment to bioanalytical method validation report. The LT study was performed for 167 days at -20ºC and -70ºC.
- SOP on Staff Training and review of training schedule.
- Compliance with relevant SOP requirements was assessed regarding performance of system suitability testing and system performance assessments prior to each analytical run.
- Review of batch processing documentation and analytical run data in paper and electronic format (Analyst software version 1.4.2) for a number of subject samples. Assessment of IS response reviewed, data acquisition times reviewed, recovery of CCs and QCs assessed and acquired sample concentrations verified against the associated tables in the analytical study report.
- Compliance with the requirements of the standard testing procedure was assessed for analytical batch processing and analysis.
- Issues with analytical runs and subsequent investigation reports were reviewed and the associated sequences of events were followed for appropriateness and completeness.

For last two days, inspectors focused to the clinical part of the study and inspected following areas:

- Recruitment and screening of volunteers. At the time of the inspection, a password protected excel sheet was used to maintain the volunteer database. In addition, a separate excel sheet was maintained to check participation of volunteers in last study and also other studies. Beside this, the CRO reviewed the on-line volunteer information system (OVIS) to verify cross participation of volunteers at other CROs in the vicinity of Ahmedabad.
- A volunteer tracking sheet was maintained. The screening validity is of 21 days.
- Screening activity comprised of body mass index, x-ray, ECG and blood sample collection
- There were 4 cabins used for the informed consent which is recorded through CCTV system.
- For the ECG, it has been noted that since the last WHO inspection held in March 2012, the CRO had removed old ECG machine and replaced with GE machine which does not store any data as claimed. In addition, Cadila have introduced logbooks to record when the ECG machine is used during the day (start and end times) and a logbook to record which subjects ECGs are captured at which times and on which dates (for screening activities)
- Tour of clinical facility
- Special contingency insurance policy
- Application for ethical review of research proposal
- IEC composition and approval letter and minutes of meeting
- SOP on Finance and Insurance of Study Volunteers During Clinical Studies
- Review of IMP administration records against the study randomisation schedule for subjects
- Review of blood sample collection records and correlation of missing samples against the sample analysis records.
- Review of staff attendance records,
- Review of in clinic forms and logs against relevant CRF data (meal consumption, screening numbers, subject dates of birth, calculation of BMI, subject height, subject weight, drugs of abuse test results, alcohol detector usage log (also showing relevant test results)).
- Volunteer registration form
- Review of case report form (CRF) of subjects
- SOP on administration of investigational products
- Verification of ECG memory detail with GE service engineer
- Verification of x-rays for subjects
- Shipping documents for investigational product (IPs) and temperature record of IPs
- IPs accountability form, reconciliation of IPs
- Closed meeting between inspectors
- Exit meeting with site representatives

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

This part of the trials was found to be satisfactory overall for the study examined and for the facilities. Some recommendations were made and appropriate actions were initiated.

2.2. THE PROTOCOL

In general, the protocol submitted to IEC along with CV of the PI, ICF in English and Vernacular language were found appropriate. From the study documents, it was found that the protocol was adequately followed during the course of study being conducted.

2.3. PROTECTION OF TRIAL SUBJECTS

There were some issues noted which were adequately addressed and will be verified during future inspections.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

In general, this area met the GCP requirement. The observation raised from this section was addressed satisfactorily and will be verified during future inspections.

2.5. RESPONSIBILITIES OF THE SPONSOR

It was found that the study was not monitored by the sponsor for any period. The observation raised from this section was addressed satisfactorily and will be verified during future inspections.

2.6. RESPONSIBILITIES OF THE MONITOR

The monitor has not fulfilled their responsibility. The observation raised from this section was addressed satisfactorily and will be verified during future inspections.

2.7. MONITORING OF SAFETY

Safety was found to be adequately monitored by the CRO. The observation raised from this section was addressed satisfactorily and will be verified during future inspections.

2.8. RECORD-KEEPING AND HANDLING OF DATA

In general, this area was found to be acceptable.

2.9. STATISTICS AND CALCULATIONS

This area was not inspected.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

There were some ambiguities noted on the proof of purchase for the reference product. The issue has been escalated to sponsor directly. The observation raised from this section was addressed satisfactorily and will be verified during future inspections.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

This was not covered within the scope of this inspection.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

This area was generally satisfactory; however some observations were raised, and addressed adequately. The observation raised from this section was addressed satisfactorily and will be verified during future inspections.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the study # 0211/006 (*A Randomized, Open-label, Two-treatment, Two-period, Two-sequence, Single dose, Two-way crossover bioequivalence study of Ondansetron Hydrochloride 8 mg tablet (containing Ondansetron Hydrochloride dehydrate eq. to Ondansetron 8mg) of Cadila Pharmaceuticals Ltd., India compared with Zofran 8mg tablets (containing Ondansetron Hydrochloride dehydrate eq. to Ondansetron 8mg) of GSK procured from Switzerland, in Healthy, adult, human subjects under fasting condition*) was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at Cadila Pharmaceuticals Ltd (CRO), Ahmedabad, Gujarat, India.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the CRO, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.