CARBAMAZEPINE – PROTOCOL DEVELOPMENT FOR ANDA SUBMISSION UNDER FDA

A Dissertation Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI – 600 032.

In partial fulfilment of the requirements for the award of the Degree of

MASTER OF PHARMACY

IN

BRANCH - IV - PHARMACOLOGY

Submitted by

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NOVEMBER 2019

CERTIFICATE

This is to certify that this dissertation entitled **"CARBAMAZEPINE - PROTOCOL DEVELOPMENT FOR ANDA SUBMISSION UNDER FDA"** submitted by **Ms. S.ISWARYA** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the degree of **MASTER OF PHARMACY IN PHARMACOLOGY,** is a bonafide work carried out by the candidate under my guidance and supervision in the Department of Pharmacology, R.V.S College of Pharmaceutical Sciences, Sulur, Coimbatore-641 402.

I have fully satisfied with her performance and work. I have forward this dissertation work for evaluation.

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EVALUATION CERTIFICATE

This is to certify that this dissertation entitled **"CARBAMAZEPINE - PROTOCOL DEVELOPMENT FOR ANDA SUBMISSION UNDER FDA"** submitted by **Ms. S.ISWARYA** bearing **Reg.No.261725655** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the degree of **MASTER OF PHARMACY IN PHARMACOLOGY,** is a bonafide work carried out during the academic year 2017-2019 by the candidate at, Department of Pharmacology, R.V.S College of Pharmaceutical Sciences, Sulur, Coimbatore and was evaluated by us.

Examination centre:

Date:

Internal Examiner **External Examiner**

DECLARATION

I hereby declared that this dissertation work entitled **"CARBAMAZEPINE - PROTOCOL DEVELOPMENT FOR ANDA SUBMISSION UNDER FDA"** submitted by me, in partial fulfilment of the requirements for the degree of **MASTER OF PHARMACY IN PHARMACOLOGY,** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, is the result of my original and independent research work carried out under the guidance of **Dr. BENITO JOHNSON M.Pharm.,Ph.D (**Institutional Guide) Professor, HOD of Pharmacology in R.V.S. College of Pharmaceutical Sciences, Sulur, Coimbatore and **Mr. MURUGAN PANCHATCHARAM** (Industrial Guide) VP, AMARIS CLINICAL, Chengalpattu.

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ACKNOWLEDGEMENT

I am delighted to thank all of those who helped and supported me to complete this project work successfully.

I express my sincere and deep sense of gratitude to my guide **Dr. Benito Johnson, M.Pharm., Ph.D,** Department of Pharmacology, R.V.S college of Pharmaceutical Sciences, Coimbatore, for his transcendent suggestions, constructive criticism , constant encouragement and his best guidance makes me to prepare a good thesis.

My heartfelt and sincere thanks to **Mr. Murugan Panchatcharam M.Pharm,** VP, Amaris Clinical, Chengalpattu, for given me the opportunity to perform my thesis in their CRO and grateful for his support from conceptualization of the project work to the preparation of the thesis.

I sincerely extend my thanks to **Dr. Venkatanarayanan, M.pharm, Ph.D,** Principal, R.V.S college of Pharmaceutical Sciences, Coimbatore, for encouraging and permitting me to carry out the project work at CRO.

My sincere thanks to **Mr. Joseph Kamalesh,** President, Amaris Clinical, Chengalpattu, who gave me opportunity to do my thesis in their CRO.

My respectful and deep sincere thanks to **Mr.C.Balachandar M.Pharm,** Amaris Clinical (MWG Dept.), Chengalpattu, who supervises me throughout the preparation of my thesis. It's impossible to complete my thesis work without his guidance.

I am pleasure to thank **Ms. M. Arul Selvi MSc.** (Clinical Trial), Amaris Clinical (MWG Dept.), Chengalpattu, who provides many relevant details regarding my project work and supports me for streamling my thesis work. She have been very helpful to me for the completion of my project work.

My deep heartfelt thanks to **Mr. G. Ramachandran MSc.,** (Medical Pharmacology), Amaris Clinical (PMT Dept.), Chengalpattu, who taught me basics about working operations in CRO and delivered many ideas regarding my thesis work.

My sincere thanks to **Mr.Suresh, Ms. Shiny, Mr. Akhil Vasudevan,** Assistant Professors of Pharmacology, R.V.S College of Pharmaceutical Science, Coimbatore, for their support throughout my thesis work.

A special thanks to **Dr. Anusuya, Mr. Vinoth Kumar, Mrs. Anitha, Ms. Kalpana, Mr. Balaji, Ms. Pallabini, Mr.Dhinakaran, Ms.Nithya, Ms. Sabeetha** who are employees of Amaris Clinical, supports me during the entire period of my work.

I express my wholehearted thanks to my close friends **Mr. M.Vijay Janaki Raman, Mrs.D.Archana, Mrs.Gowri Narayani, Mrs.Saheedha, Mrs.Habeeba, Mr.Mangalaselvan, Mr.Ranjith, Mr. Muhammed Fasil, Mr. Vahab, Ms.Tamil Vani** for their continuous encouragement and support.

I want to thank especially **my father, my mother, my sister** for their lovable affection, prayer, encouragement and sacrifices which makes me to work sincerely and inspires me to give the best work.

TABLE OF CONTENTS

ABBREVIATIONS

ANDA	Abbreviated New Drug Application
AC	Amaris Clinical
AE	Adverse Event
BE	Bioequivalence
CI	Clinical investigator
CPG	Clinical Pharmacology
DCGI	Drug Controller General of India
EC	Ethics Committee
EMA	European Medicine Agency
IT	Information Technology
ICH	International Council for Harmonisation
IRB	Institutional Review Board
LA	Licensing Authority
MWG	Medical Writing
NIH	National Institute of Health
No:	Number
NTI	Narrow Therapeutic Index
PI	Principal Investigator
PMT	Project Management
QAU	Quality Assurance Unit
SAE	Serious Adverse Events
SOP	Standard Operating Procedures
TMF	Trial Master File
USFDA	United States Food and Drug Administration
WHO	World Health Organisation

INTRODUCTION

1. INTRODUCTION

Contract Research Organization (CRO)

- A Contract Research Organisation, also called Clinical Research Organization (CRO) is a service organization, provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.[1]
- CRO provide services such as biopharmaceutical development, biological assay development, commercialization, preclinical research, clinical research, clinical trials management, and pharmacovigilance.
- CROs also support private research foundations, research institutions, and universities, in addition to governmental organizations such as the NIH, EMA, etc.
- CROs are designed to reduce costs for companies developing new medicines and drugs in niche markets. They aim to simplify entry and development of drugs into drug markets.
- The studies in CRO must be carried out to the highest professional standards and should be compliance with ICH and Good Clinical Practice guidelines.[2]
- Specifically pertaining to CROs providing clinical-trial services, the International Council for Harmonisation of technical requirements for registration of pharmaceuticals for human use(ICH-GCP) (E6) (R2) defines a Contract Research Organization (CRO) as:

"A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions."

- As per (ICH-GCP) (E6) (R2) defines, a Sponsor as[3]

"An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial."

- The main roles of sponsor are,
  - The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

- Agreements, made by the sponsor with the institution and any other parties involved with the clinical, should be in writing, as by a legal agreement. Ensure that handling of data from each stage is reliable and have been processed correctly.
- Any study-related duty and function that is transferred to and assumed by a CRO should be specified in writing.[4]

FUNCTIONS OF VARIOUS DEPARTMENTS IN CRO

Clinical Department:[5-9]

- To oversee the medical aspects of the studies with regard to subject safety and responsible for planning, start-up, conduct and close out of the clinical studies.
- Involved in the day-to-day activities and is usually the largest and most dynamic group.
- It consists of clinical research associates, project managers, clinical study assistants, etc. who monitors the clinical studies.
- Their main responsibilities are,
    - Preparation and control of research budgets and financial payments.
    - Prepare advertising and other educational materials and conduct campaigns to enrol subjects.
    - Enrol subjects in the study as per the study protocol.
    - Manage subject registration to make sure that informed consent is effectively obtained.
    - Notify subjects regarding all study aspects relevant to them.
    - Determine dosages, dispense drugs to subjects, and deliver instructions as necessary.
    - Keep track of study activities to make sure compliance with protocols and with all related local, state, and national regulatory and institutional polices.
    - Overview proposed study protocols to assess factors such as sample collection procedures, data management issues, and possible subject threats.
    - Manage necessary records of study related activity which includes case report forms, drug dispensation records etc.
    - Monitor enrolment status of participants and record dropout details such as dropout causes and subject contact efforts.
    - Record adverse event and side effect information and consult with investigators concerning the reporting of events to regulatory agencies.

- Enter study data into the applicable database.
- Direct the request, collection, labelling, storage, or shipment of samples.
- Involved in quality assurance audits performed by study sponsors, regulatory authorities, or exclusively designated review group.

Medical Writing:

Medical writers closely associated with regulatory department in preparing narratives for submission and mainly involved in writing of,

- Promotional material
- Clinical Study Protocol
- Clinical Research Standard Operating Procedure
- Clinical Research Report
- Clinical Research Abstract and Excerpt Writing
- Writing Case Reports Forms
- Documentation for Regulatory Submission
- Technical Documentation for Clinical Studies
- e-learning Modules Writing

Bioanalytical Department:[10-11]

- Quantitative measurement of a compound (drug) or their metabolite in biological fluids
- The two main components in Bioanalytical method are Sample preparation and Detection of the compound.
- A validated bioanalytical method should be compliance with Good Laboratory Practices (GLP).
- Validation parameters should be evaluated for quantitative procedures: selectivity, calibration model, stability, accuracy (bias, precision) and limit of quantification. Additional parameters which include limit of detection (LOD), recovery, reproducibility and ruggedness (robustness).
- It is generally accepted that sample preparation and method validation are required for the reliability of the analytical results. They provides,
  - Method development, optimization and validation of PK/PD assays
  - Study design
  - High-throughput sample analysis (PK, PD and biomarkers) in a GLP-certified laboratory
  - Flexible data management system with custom-made result reports

Biostatistics:

- Responsible for all statistical aspects of the clinical protocol
- Provide statistical consultation for clinical protocol design, conduct, efficacy evaluation and data review
- Analyze and report on clinical study data
- To figure out whether the study has yielded positive or negative results.

Data Management:

Large role to facilitate proper data entry and responsible for the quality and integrity of the clinical data into the database. Ensure that the data collected from clinical studies is clean and ready for analysis. To achieve this they use sophisticated software's like Oracle Clinical, SAS Pheed IT and Open Clinica etc.

The role of data manager is to,

- Design/validate/maintain clinical database
- Review data in clinical database with regard to quality and integrity
- Generate queries to the non-conformant data or data requiring clarification
- Train site personnel

Quality Assurance:

- Ensuring that a study is conducted as per regulations and guidelines put forth by the regulatory authorities, and per company Standard Operation Procedure (SOP).
- Ensure that the study compliance with the GCP guidelines.
- Maintaining version control of SOPs to ensure that all staff are following the correct and up to date SOPs.
- Quality Assurance (QA) staff is responsible for the overall quality of the organization and reviewing the protocol and reports of the study.

Regulatory submission team:

- Responsible for liaising with the regulatory authorities and manages all aspects of compliance and submissions from initiation of study to conduct to application of market approval.
- Review study documents such as Protocols, Informed Consents, Investigator Brochures, study and site-level regulatory documents for completeness/accuracy per regulations/guidelines.
- Submission of various documents and obtaining approvals from regulatory authorities like the DCGI.

- Submitting the protocol and consent documents to the IRB and making any changes in those documents required by the IRB.
- Distributing the IRB-approved protocol and consent documents, to the participating CRO and to assist the staffs in preparing their IRB submissions regarding clinical studies.
- Providing regulatory guidance to the study sites as necessary. This responsibility continues throughout the duration of the study.
- Ensures that regulatory documents comply with the relevant guidelines and that the content of the document is accurate and reflects information/data in the source documentation.

IT Team:[5]

Purchase and maintenance of IT related needs like desktops, laptops, servers, telephones, software's etc.

Admin and Finance:

Takes care of all administration and finance related work.

Human Resources:

Responsible for hiring new staff and developing measures to retain talent pool in the organization.

Training & Development:

Conducts routine trainings to ensure that the staffs remain skilled and up to date with recent advances and focuses on the professional development of its employees.

ABOUT AMARIS CLINICAL

Amaris clinical (AC) is established as a research division of Caplin point laboratories Ltd., and is located at No.44, 8th Avenue, Mahindra World City, Chengalpattu, Tamil Nadu- 603004.

The primary scope of the research division is to conduct Bioequivalence studies in healthy human volunteers for Generic Pharmaceuticals of Caplin Point Laboratories Ltd.,in some cases of generic drugs where the bioavailability cannot be demonstrated in bio-samples a clinical endpoint study will be used to demonstrate equivalence to the innovator product. For certain classes of drugs like cytotoxic and psychotropic drugs, BE studies can be done only on appropriate patients. These studies will be executed at hospital sites and centrally controlled by Amaris Clinical division.

A bioavailability/bioequivalence (BA/BE) study is conducted to assess the equivalence between two products such as a commercially available Brand product and a potential to-be-marketed Generic product.

Generic drug products developed by Caplin point Laboratories Ltd., will be subjected to BA/BE study in this division. The facility and the procedures are designed in such a way to meet all national and international regulatory requirements. Amaris clinical is capable of performing studies for submission in different regulatory markets like USA, Europe, Japan, Canada, Australia, Colombia, Brazil etc., in strict adherence to regulatory requirements by regulatory authorities including USFDA, ICH, WHO.

BA/BE studies are conducted in healthy human volunteers. The volunteers are administered with the test and reference product in randomised order and blood samples are collected in pre-defined time intervals. The collected samples are assayed for the quantity of the drug product present in each time point. Based on the concentration in different time intervals, the absorption and elimination profile for test and reference product will be established. Statistical analysis will be performed for the results to determine if the test product is equivalent to the reference product.

All the activities are performed based on a protocol specific to each project which is pre-approved by an Ethics Committee and Licensing Authority. All the activities and results will be summarised in the form of a report and submitted for regulatory approval.

In Amaris clinical, there are four major departments, **Clinical Pharmacology**, **Bio analytical**,

Biometric Services (Medical Writing, Biostatistics and Clinical Data Management) and Quality Assurance Unit along with other supporting departments.

Confidentiality: The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Clinical studies and Bio-analysis conducted in accordance with Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) respectively. Quality assurance Systems with procedures that assure the quality of every aspect of the study should be implemented.

GENERAL TERMS AND DEFINITONS[3]

Adverse Drug Reaction (ADR):

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reaction.

Adverse Event (AE):

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Audit:

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Case Report Form (CRF):

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study:

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

Good Clinical Practice (GCP):

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Independent Ethics Committee (IEC):

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Informed Consent:

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Institutional Review Board (IRB):

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Investigational Product:

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator:

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Investigator's Brochure:

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Protocol:

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

Protocol Amendment:

A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance (QA):

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC):

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomization:

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Regulatory Authorities:

Bodies having the power to regulate. In the ICH GCP Guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Serious Adverse Event (SAE):

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- results in congenital anomaly/birth defect.

Sponsor:

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Standard Operating Procedures (SOPs):

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Subject/Trial Subject:

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Unexpected Adverse Drug Reaction:

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Vulnerable Subjects:

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

PRINCIPLES OF ICH GCP[12]

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

BIOAVAILABILITY:[15]

Bioavailability means the rate and extent to which the active drug substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action.

BIOEQUIVALENCE:

Bioequivalence is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study".

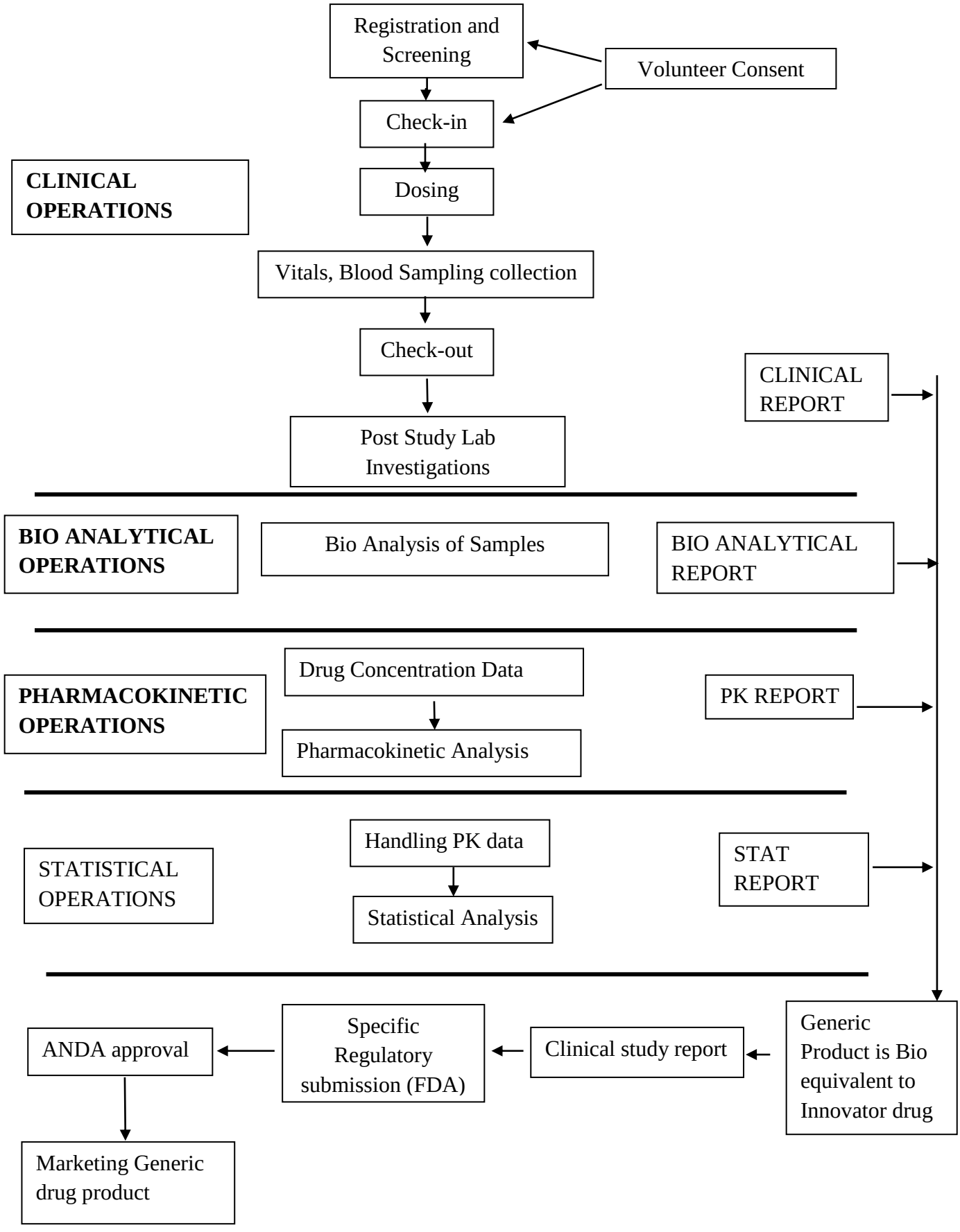
BA/BE STUDIES:[14-16]

Bioavailability (BA) and bioequivalence (BE) studies play a major role in the drug development phase for both new drug products and their generic equivalents, and thus attract considerable attention globally. The generic drugs would be interchanged with innovator products in the market place, it must be demonstrated that the safety and efficacy of generics are comparable to the safety and efficacy of the corresponding innovator drugs. BE is a strategy to introduce generic equivalents of brand-name drugs (innovator drugs) to lower the cost of medication through proper assessment as directed by the regulatory authorities. There are several approaches to assess BE and each regulatory authority has its own regulations/guidance for conducting BA/BE studies before approving generic products for marketing in their country.

The general considerations for the advancement of conducting BA/BE studies are:

- Study design and protocol
- Bioanalysis
- Selection of appropriate analyte(s)
- BE metrics and data treatment
- Statistical approaches and analysis
- Acceptance criteria for BE

WORKING OPERATONS IN BA/BE STUDIES



Regulatory authorities to harmonize approaches for bioequivalence assessment:

Every country now has its own regulatory authority as well as regulatory guidance for BA/BE studies, and the magnitude of assessment of BE of drug product is influenced by the regulatory environment of the respective country for marketing. Some of them are;

COUNTRY	REGULATORY AUTHORITY
INDIA	Central Drugs Standard Control Organization (CDSCO)
UNITED STATES	Food and Drug Administration (FDA or USFDA)
EUROPE	European Medicines Agency (EMA)
CANADA	Health Canada
BRAZIL	National Health Surveillance Agency (ANVISA)
COLOMBIA	Colombia National Food and Drug Surveillance Institute(INVIMA)
UNITED KINGDOM	Medicines and Healthcare products Regulatory Agency
AUSTRALIA	Therapeutic Goods Administration (TGA)
CHILE	Institute of Public Health
SWITZERLAND	Swiss Agency for Therapeutic Products

FOOD AND DRUG ADMINISTRATION [17-18]

The Food and Drug Administration (FDA or USFDA) is a federal agency of the United States Department of health and human services, one of the United States federal executive departments.

In 1984, United States Congress passed the "Drug Price Competition and Patent Term Restoration Act of 1984" that authorized FDA to approve generic drug products through BA and BE studies. As a result of the passage of this act, several activities were initiated by the FDA for the review and approval of generic drug application (Abbreviated New Drug Application, commonly known as ANDA). During 1984 to 1992, FDA published for the industry a series of drug-specific BA/BE guidance's, general guidance on conducting studies, and regulatory recommendations and statistical guidance to document BE. Consequently, these guidance's helped the industry to conduct BA/BE studies and receive approval of a large number of generic drug products.

The Food and Drug Administration (FDA) is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply cosmetics, prescription and over-the-counter pharmaceutical drugs, transfusions, medical devices, electromagnetic radiation emitting devices (ERED), and animal foods & feed. The FDA also provides accurate, science-based health information to the public.

FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

EUROPEAN MEDICINES AGENCY [19-20]

The European Medicines Agency (EMA) is a European Union agency for the evaluation and supervision of medicinal products. Prior to 2004, it was known as the European Agency for the Evaluation of Medicinal Products or European Medicines Evaluation Agency (EMEA).

The EMA was set up in 1995 with funding from the European Union and the pharmaceutical industry, as well as indirect subsidy from member states, in an attempt to harmonize (but not replace) the work of existing national medicine regulatory bodies. The EU is currently the source of about one-third of the new drugs brought onto the world market each year.

The EMA operates as a decentralized scientific agency (as opposed to a regulatory authority) of the European Union and its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

Its scope of operations is medicinal products for human and veterinary use including biologics and advanced therapies, and herbal medicinal products.

The agency is composed of the Secretariat, a management board, seven scientific committees (human, veterinary, herbal medicinal products, orphan drugs, pediatrics, advanced therapies and pharmacovigilance risk assessment) and a number of scientific working parties.

The Secretariat is organized into five units:

Directorate, Human Medicines Development and Evaluation, Patient Health Protection, Veterinary Medicines and Product Data Management, Information and Communications Technology and Administration.

HEALTH CANADA (TPD and BGTD)

Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD) respectively, regulate pharmaceutical drugs, medical devices, biological drugs and radiopharmaceuticals for human use.

Canadian regulatory authorities were the first to apply pharmacokinetics (PK) to safety and efficacy risk assessment of generic drug products following the 1969 amendments to the Patent Act. Formal guidelines were subsequently developed in the 1990s by an Expert Advisory Committee (EAC) where the latest name iteration is the Scientific Advisory Committee (SAC) on Pharmaceutical Sciences and Clinical Pharmacology (SAC-PSCP) which continues to provide advice towards producing several interim guidances and policies into the new millennium.

Health Canada is thus the official Canadian agency that requests, analyses and recognizes bio equivalency of Canadian generic drug products targeted for the Canadian market. Health Canada is responsible for the maintenance and improvement of Canadians health. It ensures that high-quality health services are accessible, and works to reduce health risk.

COMPARISON OF REGULATORY REQUIREMENTS (USA, EUROPE, HEALTH CANADA)

FOR BA/BE STUDIES[21-25]

Sr. No.	Parameters	Division	USA	Europe	Canada
1.	GCP requirements		ICH-GCP guidelines	ICH-GCP guidelines	ICH-GCP guidelines
2.	Study design		Non-replicated, randomized, crossover studies	Non-replicated, randomized, crossover studies	Non-replicated, randomized, crossover studies
3.	Type of study (Condition)		Fasting and fed	Fasting	Fasting
4.	Volunteers		Sufficient to achieve adequate power	>12 (Min 80% power of acceptance criteria)	Min 80% power of acceptance criteria
5.	Sex		Both Male and Female	Both Male and Female	Both Male and Female
6.	Age		18 years or older	18 years or older	18 – 55 older
7.	Body Mass Index (BMI) (kg/m^2)		18.5-24.9	18.5-30	18.5-30
8.	Study dose	Test	Made by the manufacturer	Made by the manufacturer	Made by the manufacturer
		Reference	Reference listed drug in USA	European reference product	Canadian reference product

Sr. No.	Parameters	Division	USA	Europe	Canada
9.	Type of study	Immediate Release	1 single dose crossover study fasted 1 single dose crossover study fed (if food is mentioned in the product) If a multiple-dose study design is important, appropriate dosage administration and sampling be carried out to document attainment of steady state.	1 single dose crossover study, fasted. Or fed condition according to Summary of Product Characteristics.	Fasting
		Modified Release	Fasting, fed and steady state.	Fasting, fed and steady state	Fasting, fed and steady state
10.	Sample size (minimum)		12	12	12
11.	Sampling points		12-18 samples per subject/dose	Sufficient number of samples, at least 2 samples before expected T_{max}, 3–4 terminal log–linear phase	Minimum 12 samples per subject/dose
12.	Washout period		More than 5 half-lives of the moieties to be measured	For Steady State; at least 5 times the terminal half-life	Not less than 10 times the mean terminal half-life of the drug

Sr. No.	Parameters	Division	USA	Europe	Canada
13.	Fasting Criteria		At least 10 hours prior to administration of the products and no food is allowed for at least 4 hours post-dose.	At least 08 hours prior to administration of the products and no food is allowed for at least 4 hours post-dose.	At least 10 hours prior to administration of the products and no food is allowed for at least 4 hours post-dose.
14.	Fed study Requirements	Total	800-1000 calories	800-1000 calories	800-1000 calories
		Protein	150 calories	150 calories	150 calories
		Carbohydrate	250 calories	250 calories	250 calories
		Fat	500-600 calories	500-600 calories	500-600 calories
15.	Diet	Fasting	No food is allowed for at least 4 hours post dose	No food is allowed for at least 4 hours post dose	No food is allowed for at least 4 hours post dose
		Fed	Subjects should start the meal 30 minutes prior to administration of the drug product and eat the meal within 30 minutes	Subjects should start the meal 30 minutes prior to administration of the drug product and eat the meal within 30 minutes	Subjects should start the meal 30 minutes prior to administration of the drug product and eat the meal within 30 minutes
16.	Fluid intake		Subjects should be administered the drug product with 240 mL (8 fluid ounces) of water. Water is allowed as desired except for one hour before and one hour after drug administration	Subjects should be administered with a standardised volume of fluid (at least 150 mL). Water is allowed as desired except for one hour before and one hour	Subjects should be administered with a standardised volume of fluid (at least 150 mL). Water is allowed as desired except for one hour before and one hour after drug

Sr. No.	Parameters	Division	USA	Europe	Canada
				after drug administration	administration
17.	Moieties to be measured in plasma		Active drug/metabolites if applicable	Active drug/metabolites if applicable	Active drug/metabolites if applicable
18.	Analytical method validation parameters		Accuracy, precision, selectivity, sensitivity, reproducibility, calibration curve, Lower Limit of Quantification(LLOQ) and stability	Accuracy, precision, repeatability, intermediate precision specificity, limit of quantitation, linearity range	Stability, Limit of Quantification (LOQ), specificity, recovery, standard curves, precision and accuracy
19.	Pharmacokinetic parameters		C_{max}, T_{max} AUC_{0-t} and $AUC_{0-\infty}$, $t_{1/2}$, λ_z	C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$, $t_{1/2}$, λ_z	C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$, $t_{1/2}$, λ_z
20.	Criteria for bioequivalence (Confidence Interval)		(90% CI)80.00–125.00% forC_{max} , AUC_{0-t}, $AUC_{0-\infty}$	(90% CI) 80.00–125.00% forC_{max}, AUC_{0-t}, $AUC_{0-\infty}$	(90% CI) 80.00–125.00% forC_{max} , AUC_{0-t}, $AUC_{0-\infty}$
21.	90 % confidence interval on Log transformed data	C_{max} %	80-125	80-125	80-125
		AUC_{0-t}%	80-125	80-125	80-125
		$AUC_{0-\infty}$%	80-125	Not Applicable	Not Applicable

Sr. No.	Parameters	Division	USA	Europe	Canada
22.	Narrow therapeutic index drugs (90 % confidence interval)	Cmax %	90.00 – 111.11	90.00-111.11	80.00 – 125.0
		AUC_{0-t}%	80.00 – 125.0	90.00-111.11	90.00– 112.0
23.	Highly variable drugs (90 % confidence interval)	Cmax %	Geometric Mean Ratio (GMR) [80 -125]	69.84 – 143.19	80.00 – 125.00
		AUC_{0-t}%	GMR (80 -125)	80-125	80.00 – 125.00
24.	Linear Pharmacokinetics		Reference Listed Drug (RLD) in the Orange Book usually the highest strength is preferred if formulations are proportionally similar	The bioequivalence study should in general be conducted at the highest strength. Highly soluble drug and any safety concern: Lower strength acceptable. Problems of sensitivity of the analytical method: Highest strength acceptable	Use strength with largest sensitivity to identify differences in formulation

Sr. No.	Parameters	Division	USA	Europe	Canada
25.	Non Linear Pharmacokinetics		Reference Listed Drug (RLD) in the Orange Book	In most cases, bioequivalence be established both at the highest strength and at the lowest strength	The lowest strength (single dose unit) in the fasted state and the highest strength in both the fasted and fed states

AIM AND OBJECTIVES

2. AIM AND OBJECTIVES

AIM

To design and develop Protocol for Carbamazepine, for ANDA submission under FDA.

OBJECTIVES

- To discuss about the Protocol and Medical Writing Department.
- To explain the Types, Causes, and Mechanism of Epilepsy.
- To describe the steps for Literature search, Study design, Sampling times and Washout interval for Protocol preparation in BE studies.
- To Prepare a Protocol for ANDA submission under FDA.

LITERATURE REVIEW

3. LITERATURE REVIEW

Agarwal D, *et al*., (2005)[26] explained on theeffect of sampling schedule and size in the determination of rifampicin bioequivalence in a three-drug fixed dose combinations by WHO and Indian protocols. Finally,it was concluded that minimising sample size after validation and poor quality FDC formulations can further reduce the cost of conducting bioequivalence studies.

Panchagnula R *et al.*, (2003)[27] evaluates whether the WHO simplified screening protocol for the bioequivalence assessment of rifampicin can be used for the evaluation of isoniazid and pyrazinamide of three and four drug fixed dose combination so as to ensure the bioavailability of all drugs at tissue site. After evaluation of isoniazid and pyrazinamide based on their pharmacokinetic parameters, it was found that C_{max} affected by limited sampling time points of WHO protocol. Further, AUC was a robust parameter unaffected by sampling schedule adopted. Thus, the WHO simplified protocol for assessment of rifampicin is also suitable for evaluating bioequivalence of isoniazid and pyrazinamide from FDC formulations. However, for comparison of rate of absorption by means of C_{max}, careful evaluation of concentration-time profile along with pharmacokinetics is necessary before final judgment.

PROTOCOL:[3]

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

PURPOSE FOR THE PROTOCOL:[28-29]

The most difficult stage of conducting a clinical study is the preparation of a protocol that results in a short yet comprehensive document that clearly summarizes the study. It is important to develop a protocol in order to perform an appropriate study and obtain reliable results. Good protocol will save failures at a later stage besides helping analysis.

Clinical research is conducted according to a Protocol (a plan). The protocol demonstrates the guidelines for conducting the study. The protocol and its attachments should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology, criteria for acceptance of bioequivalence, and the proposed number of participants is reasonably justified and the scientific design is adequately described.

However, once the study is launched, the protocol should not be altered during the progression of the study. If the changes during progress of the study are minor, then that part of the study should be excluded from the analysis. Unless unexpected complications occur during the conduct of the study, it is advisable to reconsider and rewrite the protocol where the whole process is started again provided that the original research topic is still considered to be relevant. If complications are anticipated, it is suitable to conduct a pilot study, to evaluate the feasibility prior to perform the pivotal study.

BENEFITS OF THE PROTOCOL:

It serves as a guide throughout the study and estimates the duration and budget for the study.

The nature and extent of any benefits is to be achieved by ensuring,

- The safety and well-being of the study subjects,
- The rights and dignity of the study subjects,
- The successful completion of the study,
- The credibility of the data collected,
- The research should deliver enormous benefits to the society,
- The safety and wellbeing of the research team.

PROTOCOL REVIEW:

Initially, the protocol is reviewed by major departments of the CRO. The clinical study plans can be developed by there commendations and suggestions from the colleagues and experts.

Clinical study must be approved and monitored by an Institutional Review Board that ensures that the risks are negligible and are worth any potential benefits. It is an independent committee that consists of physicians, dentists, statisticians, and members of the community.

The committee ensures that clinical studies are ethical and that the rights of all participants are protected. The board must initially approve the study by the protocol review and periodically review the clinical study.

Before commencing the study, consultation with Research Ethics Committees, Research and Development offices and other regulators will determine whether the protocol is appropriate for the clinical study.

MEDICAL WRITING:[30-33]

The success of Medical writing in clinical research depends upon the proper documentation and the exactness of the research, its planning and results.Medical writing involves writing scientific documents of different types which include regulatory and research related documents, disease or drug-related, familiar with searching medical literature, understanding and presenting research data, and document review process and editing.

Medical and regulatory documentation developed by experienced medical writing teams plays a pivotal role in the success of a clinical research. Medical writing team works closely with operational departments including Biostatistics, Regulatory affairs, Quality Assurance, and Clinical Operations to access a fully network of information.

Contract research organisations provide many different writing opportunities across the clinical development phases, from clinical research protocols to reports, manuscripts, patient information sheets and informed consent forms.

Writers can be involved in preparing the protocol, the accompanying informed consent form and the subsequent clinical study report for a study and so be involved in the clinical study from the start-up activities onwards.

Writing a research protocol is probably one of the most challenging and difficult task for medical writers. Medical writers have close contact with the biostatistics group, who provide them study results and also helps them in data issues which they may spot during the preparation of the study reports.

ROLES OF MEDICAL WRITER:

Medical writers have important roles in preparing the documentation for approval for marketing of new products, writing manuscripts for publication, and other nonclinical, clinical, and promotional materials.

They should provide the scientific or medical information in a clear and concise manner and should familiar with the principles of clinical research.

They should have both technical and non-writing-specific skills (therapeutic and statistical knowledge).

They should prepare scientific documents of highest quality meeting all applicable regulatory requirements. They prepare documents such as,

- Research proposals
- Investigator brochures
- Informed consent documents
- Clinical study reports
- Clinical study protocols
- Package inserts
- Patient information leaflet
- Patient safety narratives

A key task of the Medical Writer is to be sure that all deliverables are in accordance with regulations, standards, and guidelines. The regulatory documents that the Medical Writer prepares must meet ICH, GLP, and GCP, and the regulatory authority guidelines regarding the clinical study submission.

Medical Writer must be aware of current industry practices and regulatory requirements and must update their knowledge incurrent literature, emerging science, technological developments and medical trends.

EPILEPSY:[34-45]

Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behaviour, sensations, and sometimes loss of awareness.

TYPES OF SEIZURES:

PARTIAL SEIZURE

The epileptic activity took place in any one part of the brain. Partial seizures may be classified as simple or complex.

Simple partial seizures usually involve a single part of the brain such as the motor area, sensory area, or others. A simple partial seizure doesn't involve loss of consciousness. Symptoms include:

- alterations to sense of taste, smell, sight, hearing, or touch
- dizziness
- tingling and twitching of limbs

Complex partial seizures occur in the frontal or temporal lobe with the brain and often involve other areas of the brain that affect alertness and awareness. These seizures result in daydream like states and sometimes involve unusual activities like picking at the air as if something was there, repeating words or phrases, laughing, or other activities.

Complex partial seizures involve loss of awareness or consciousness.

Symptoms include:

- staring blankly
- unresponsiveness
- performing repetitive movements

GENERALIZED SEIZURES

Generalized seizures involve the whole brain. There are six types:

Absence seizures (petit mal seizures), cause a blank stare. This type of seizure may also cause repetitive movements like lip smacking or blinking. There's also usually a short loss of awareness.

Tonic seizures cause muscle stiffness.

Atonic seizures lead to loss of muscle control and can fall down suddenly.

Clonic seizures are characterized by repeated, jerky muscle movements of the face, neck, and arms.

Myoclonic seizures cause spontaneous quick twitching of the arms and legs.

Tonic-clonic seizures (grand mal seizures). Symptoms include:

- stiffening of the body
- shaking
- loss of bladder or bowel control
- biting of the tongue
- loss of consciousness

CAUSES FOR EPILEPSY:

The epilepsy is caused due to factors like structural, genetic, infectious, metabolic, and immune. Common causes include,

- brain damage from prenatal or perinatal causes (e.g. a loss of oxygen or trauma during birth, low birth weight)
- congenital abnormalities or genetic conditions with associated brain malformations
- a severe head injury
- a stroke that restricts the amount of oxygen to the brain
- an infection of the brain such as meningitis, encephalitis or neurocysticercosis
- a brain tumour
- certain genetic syndrome

MECHANISM FOR EPILEPSY:

The basic mechanism of neuronal excitability is the action potential; a hyper excitable state can result from increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, an alteration in voltage-gated ion channels, or an alteration of intra or extra-cellular ion concentrations in favour of membrane depolarization.

Action potentials occur due to depolarization of the neuronal membrane, with membrane depolarization propagating down the axon to induce neurotransmitter release at the axon terminal.

Epileptic activity occurs by blocking synaptic and voltage-gated inhibitory conductances, or by activating synaptic and voltage-gated excitatory conductances.

The major excitatory neurotransmitter is the amino acid glutamate. Glutamate receptors can be found post synaptically on excitatory principal cells as well as on inhibitory interneurons and have been demonstrated on certain types of glial cells.

All ionotropic glutamate receptors are permeable to Na^+ and K^+, and it is the influx of Na^+ and outflow of K^+ through these channels that contribute to membrane depolarization and generation of the action potential.

The NMDA (N-methyl D-aspartate) receptor also has a Ca^{++} channel that is blocked by Mg^{++} ions in the resting state, but under conditions of local membrane depolarization, Mg^{++} is displaced and the channel becomes permeable to Ca^{++}, influx of Ca^{++} tends to further depolarize the cell, and is thought also to contribute to Ca^{++} mediated neuronal injury under conditions of excessive neuronal activation (such as status epilepticus and ischemia), potentially leading to cell death, a process termed excitotoxicity.

The major inhibitory neurotransmitter is GABA (gamma amino butyric acid) ($GABA_A$ and $GABA_B$). $GABA_A$ receptors are found postsynaptically, while $GABA_B$ receptors are found presynaptically, and can thereby modulate synaptic release.

$GABA_A$ receptors are permeable to Cl^- ions, upon activation Cl^- influx hyperpolarizes the membrane and inhibits action potential, thus suppresses seizure activity.

$GABA_B$ receptors are associated with second messenger system which often results in opening of K^+ channels, leading to a hyperpolarization causes hyperexcitability and seizures.

NTI DRUGS:[34]

Narrow therapeutic index (NTI) drugs are drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity. FDA recommends BE standards to ensure the safety and efficacy of generic NTI drugs.

Carbamazepine is used as an anticonvulsant or anti-epileptic drug to prevent and control seizures. It is also used to relieve certain types of nerve pain such as trigeminal neuralgia.

Carbamazepine is a Narrow Therapeutic Drug.

THERAPEUTIC RANGE FOR CARBAMAZEPINE:

The conventionally accepted therapeutic range of plasma concentrations of carbamazepine in adults is 4–12 μg/mL. Serum concentrations associated with efficacy range between 1.9 and 11.7 μg/mL, though concentrations less than 4 μg/mL result in less optimal seizure control in the overall epilepsy population. AE have been reported in carbamazepine concentrations ranging from 4–19. 6 μg/mL.

METHODOLOGY

4. METHODOLOGY

CONTENTS IN THE PROTOCOL[3]

General information:

- Protocol title, protocol identifying number, and date. Any amendments should also bear the amendment number and date.
- Name and address of the sponsor and the investigator who is responsible for conducting the clinical study.
- Name of the person who is authorised to sign the protocol and the protocol amendments for the sponsor.
- Name, address and telephone number of the qualified physician who is responsible for all study related medical decisions.

Background information:

- Name and description of the Investigational Product.
- A summary from nonclinical studies which is relevant for the clinical study.
- Description and justification for route of administration, dosage, selection of subjects and treatment periods.
- References to literature and data those are relevant to the study.
- A detailed description of the objectives and the purpose of the study.

Study design:

- The design of the study should maximize the sensitivity to detect any difference between products, minimize the variability that is not caused by formulation effects and eliminate bias as far as possible. In general, for a bioequivalence study involving a multisource product and a comparator product, a randomized, two-period, two-sequence, single-dose, cross-over study conducted with healthy volunteers is the preferred study design.
- A description of the measures taken to minimize or avoid bias, including,

  Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

  Blinding: The bio-analysts performing the bio-analysis will be kept blinded for the randomization and the randomization schedule will be made available only at the time of pharmacokinetic and statistical analysis.

- A description of duration of the study, discontinuation criteria for the individual subject and the records of CRF.

Selection and withdrawal of subjects:

- Subject inclusion criteria
- Subject exclusion criteria
- A sufficient number of study subjects should be recruited, dosed appropriately, to allow for possible drop-outs or withdrawals.
- The number of subjects required for a bioequivalence study is determined by,
  - The coefficient of variation associated with the primary parameters to be studied, as estimated from a pilot experiment, or from published previous studies
  - The significance level desired (5%)
  - The statistical power desired
  - The mean deviation from the comparator product compatible with bioequivalence and with safety and efficacy
  - The need for the 90% confidence interval around the geometric mean ratio to be within bioequivalence limits, normally 80–125%, for log-transformed data.

Assessment of efficacy:

Methods and timing for assessing, recording and analysing of efficacy parameters.

Assessment of safety:

- Methods and timing for assessing, recording and analysing of safety parameters.
- Recording and reporting adverse event and intercurrent illnesses.
- The type and duration of the follow-up of subjects after adverse events.

Bioanalytical Methodology:

Evaluation of pharmacokinetic parameters should be specific, sensitive, precision and accurate.

Statistical Analysis:

The statistical method for testing bioequivalence is based on the determination of the 90% confidence interval around the ratio of the log transformed population means for the pharmacokinetic parameters under consideration and by carrying out two one-sided tests at the 5% level of significance.

List of annexure:

Annexure I – Template for Study Specific Informed Consent Form

Annexure II – Prescribing Information of Reference Product

Annexure III- Template for Case Report Form

STEPS TO SEARCH LITERATURE FOR USFDA

- Follow Food and Drug Administration (FDA) Product-Specific Guidance.
- The US Food and Drug Administration (FDA) publish a list of drug products and equivalents, Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the "Orange Book".
- Choose reference product from the orange book which serves as a standard reference for generic products.
- Search the molecule under the web Site: FDA Access Data. List of brands available in the United States (US) market will be displayed.
- Choose recommended reference product.
- Label info and labelling revisions will be available in FDA access data along with different types of reviews.
- Choose the latest label, download it and use it as an annexure to the study protocol.
- Check for Pharmacokinetic (PK) data and if found, co-relate with other information available.
- Select the "Clinical pharmacology and biopharmaceutical review" from the list of reviews displayed.
- In the "Clinical pharmacology and biopharmaceutical review", information available from studies conducted with different study designs and also for (e.g. steady state, food effect, patient based trials, single dose healthy subject data, drug interactions studies etc.,)
- The sample size can be calculated by applying ISCV value in FARTSSIE, stands for Free Analysis Research Tool for Sample Size Iterative Estimation which is an excel worksheet.
    - It was found that 86 healthy volunteers are needed for the bioequivalence study for Carbamazepine under fasting condition, by applying its 12% of ISCV value in FARTSSIE.

- In case review not available in FDA Access Data, Search for the other published literatures (e.g. Public Assessment Report (PAR) on the molecule using a web search.
- Select the relevant published literatures and look for the information of various studies conducted and published.
- In case no literatures is available, conduct a pilot study use the pilot study data for the development of pivotal study protocol.

DRUG DESIGN:[46]

Pilot study:

A pilot study is carried out in a small number of subjects before proceeding with a full bioequivalence study. The study can be used to validate analytical methodology, assess variability, optimize sample collection time intervals, and provide other information.

The pilot study that documents if the bioequivalence is acceptable, provided that its design and execution are suitable and a sufficient number of subjects have completed the study.

Cross over design:

Cross over design is most commonly used design for bioequivalence studies.

The volunteers are divided into two groups in which one group receives test product and other group receives reference product.

It was provided enough time for the elimination of the product between the medications.

The possible crossover effects can be minimised by sequence or order in which drug products are given.

Replicate cross over design:

The drugs which have intra-subject coefficient of variation more than 30% (ISCV≥ 30%),are considered as highly variable drugs, so BE studies for these drugs should be conducted for four periods due to their high variability.

This design is also conducted for narrow therapeutic drugs due to high differences in the pharmacokinetic parameters. Eg: An open label, randomized, two treatment, two sequence, four period, single dose, crossover, fully replicate, bioequivalence study of Carbamazepine (NTI drug) is recommended as per FDA.

Parallel design:

The parallel design is recommended for the drugs which have long half-life.

In parallel design, one group receives test product and the other receives reference product, which avoids carryover effects.

DESIGNING OF TIME POINTS

- In each subject, for per dose,12-18 samples should be collected including predose.
- Sampling should be taken atleast 02-05 time points during the absorption phase, 03-04 around T_{max} and atleast 03-04 during the elimination phase.
- To estimate C_{max}, time points should be clustered around T_{max} and $t_{1/2}$ is considered for the frequency of sampling during the T_{max} and for the extent of sampling.
- Consider the frequency of sampling points by plasma half-life which is 10% of the elimination half-life.

SAMPLING SCHEDULE FOR CARBAMAZEPINE

The peak plasma (t_{max}) concentration for Carbamazepine is 4-5 hrs and half life ($t_{1/2}$) is 25-65hrs. Based on $t_{max}$and$t_{1/2}$, the sampling time points are calculated in each period as,

00.00 hour (Predose), 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.33,03.67, 04.00, 04.33, 04.67, 05.00, 05.33, 05.67, 06.00, 07.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours post dose (Total of 25 samples - 03 mL each). First 22 samples will be collected in clinic and remaining samples will be collected as ambulatory.

Screening	Pharmacokinetic Analysis				Discarded blood	Post study
	Period I	Period II	Period III	Period IV		
10 ML	75 mL	75 mL	75 mL	75 mL	42 mL	06 mL

The total volume of blood draw from each subject during the study will not exceed 358 mL.

WASHOUT PERIOD

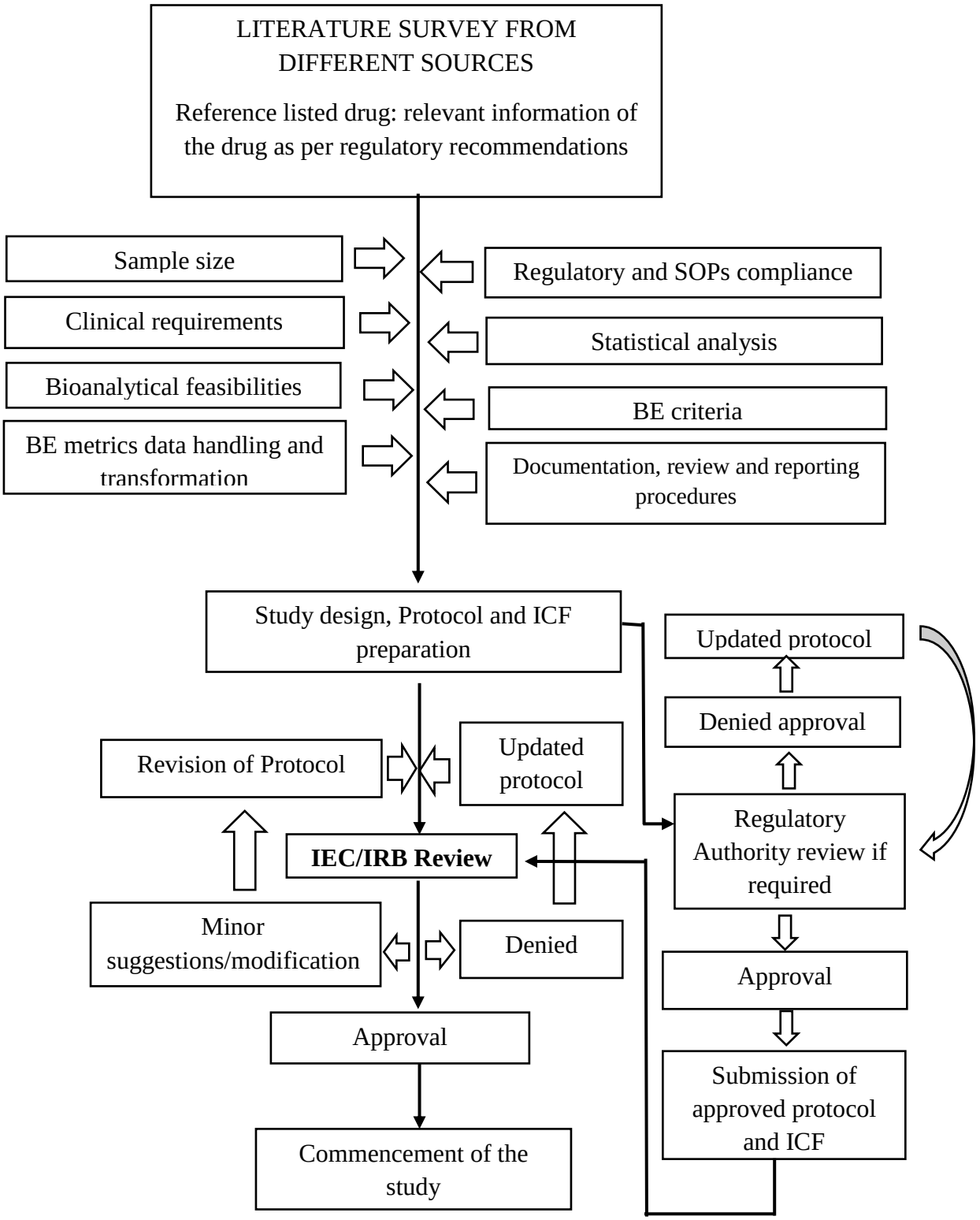
The time interval between the two treatment is called “washout period”, which is required for the elimination of the administered doses of a drug so as to avoid the carryover effect.

The washout period is calculated based on the half-life of the drug.

For FDA studies, more than 5 half-life of the drug moieties is to be measured, which is considering as a washout period.

As per FDA, the washout period for Carbamazepine is minimum 21 days. Thus, the duration of an open label, randomized, two treatment, two sequence, four period, single dose, crossover, fully replicate, bioequivalence study of Carbamazepine should take 69 days.

PROCESS FOR PROTOCOL APPROVAL IN BA/BE STUDIES



PROTOCOL

Study/Protocol Title[47-64]

An open label, randomized, two treatment, two sequence, four period, single dose, crossover, fully replicate, bioequivalence study of Carbamazepine 200mg Tablets (Manufacturer detail is confidential) and Tegretol (Carbamazepine) 200mg, Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 in healthy, adult, human subjects under fasting condition.

Project Number: AC-P-XXX-YY	Version: Draft 01	Date: YYYY-MM-DD

Sponsor Sponsor detail is confidential	**CRO** Amaris Clinical, (A Division of Caplin point laboratories Ltd) No 44, 8th Avenue, Domestic Tariff Area Mahindra World City, Chengalpattu, Tamil Nadu 603004.
Principal Investigator : XXX	
Investigational products	**Test:** Carbamazepine 200mg Tablets (Manufacturer detail is Confidential)
	Reference: Tegretol (Carbamazepine) 200mg, Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936.

1. Personnel and Facilities Involved

1.1 Sponsor

Sponsor detail is confidential

1.2 Study Centre

1.2.1 Clinical Study Facility

Amaris Clinical (A Division of Caplin Point Laboratories Ltd),

No 44, 8th Avenue, Domestic Tariff Area,

Mahindra World City, Chengalpattu, Tamil Nadu 603004.

1.2.2 X-Ray facility

Amaris Clinical (A Division of Caplin Point Laboratories Ltd),

No 44, 8th Avenue, Domestic Tariff Area,

Mahindra World City, Chengalpattu, Tamil Nadu 603004.

1.2.3 Bioanalytical Facility

Amaris Clinical (A Division of Caplin Point Laboratories Ltd),

No 44, 8th Avenue, Domestic Tariff Area

Mahindra World City, Chengalpattu, Tamil Nadu 603004.

1.2.4 Pharmacokinetic and Statistical analysis Facility

Amaris Clinical (A Division of Caplin Point Laboratories Ltd),

No 44, 8th Avenue, Domestic Tariff Area,

Mahindra World City, Chengalpattu, Tamil Nadu 603004.

1.3 Principal Investigator

XXX,

Amaris Clinical (A Division of Caplin Point Laboratories Ltd),

No 44, 8th Avenue, Domestic Tariff Area

Mahindra World City, Chengalpattu, Tamil Nadu 603004.

1.4 Clinical Laboratory Facility

XXXXX

1.5 Emergency Hospital Facility for SAE management

XXXXX

1.6 Ethics Committee

XXXXX

2. Table of Content

3. List of Abbreviations

AC	:	Amaris Clinical
AE	:	Adverse Events
ALT	:	Alanine Transaminase
ANOVA	:	Analysis of Variance
AST	:	Aspartate Aminotransferase
AUC	:	Area Under the Curve
BLQ	:	Below Limit of Quantification
BMI	:	Body Mass Index
CDSCO	:	Central Drugs Standard Control Organization
CI	:	Confidence Interval
Cmax / C_{max}	:	Concentration Maximum
CPS		Central Processing and Storage
CPGU	:	Clinical Pharmacology Unit
CTCAE	:	Common Terminology Criteria for Adverse Events
CYP	:	Cytochrome
ECG	:	Electrocardiogram
GABA	:	Gamma-aminobutyric acid
HPU	:	Human Pharmacology Unit
ICH	:	International Council for Harmonization
IEC	:	Independent Ethics Committee
K_2EDTA	:	Ethylene Diamine Tetra Acetic acid Di-potassium Salt
K_{el}	:	Terminal elimination rate constant
LLOQ	:	Lower Limit of Quantification
LSM	:	Least Square Mean
mmHg	:	Millimeters of Mercury
MSE	:	Mean Square Error
ng/ml	:	Nanograms per millilitre

PCV	:	Packed Cell Volume
PK	:	Pharmacokinetic
Rpm	:	Revolutions Per Minute
SAE(s)	:	Serious Adverse Event(s)
SAS	:	Statistical Analysis System
SD	:	Standard Deviation
T_{max} /Tmax	:	Time taken to reach maximum concentration
WHO	:	World Health Organization
WMA	:	World Medical Association

4. Study Synopsis

Title	**:**	An open label, randomized, two treatment, two sequence, four period, single dose, crossover, fully replicate, bioequivalence study of Carbamazepine 200mg Tablets (Manufacturer detail is confidential) and Tegretol (Carbamazepine) 200mg, Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 in healthy, adult, human subjects under fasting condition.
Test Product-T	**:**	Carbamazepine 200mg Tablets (Manufacturer detail is Confidential).
Reference Product-R	**:**	Tegretol (Carbamazepine) 200mg, Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936.
Name and address of the Sponsor	**:**	Sponsor detail is Confidential
Principal Investigator	**:**	XXX
Protocol Author	**:**	Iswarya. S
Study Centre	**:**	☑ Clinical | ☑ Bio-Analytical | ☑ Statistical Amaris Clinical, (A Division of Caplin point laboratories Ltd) No 44, 8th Avenue, Domestic Tariff Area, Mahindra World City, Chengalpattu, Tamil Nadu 603004.
Primary Objective	**:**	To assess the bioequivalence between the test and reference formulations.
Secondary Objective	**:**	To monitor the safety and tolerability of the drug.
Study design	**:**	An open label, randomized, two treatment, two sequence, four period, single dose, crossover, fully replicate, bioequivalence study.
Number of Subjects	**:**	86 healthy adult human male and/or non-pregnant female subjects. Subjects may be dosed in multiple divided groups on different days.

Type of study	**:**	Fasting
Number of periods	**:**	04
Washout period	**:**	Minimum 21 days
Fasting criteria	**:**	Minimum 10 hours fasting prior to dosing and 04 hours post dose.
Water restriction	**:**	01 hourpre-dose and 01 hour post-dose
Drug Administration	**:**	A single oral dose of test (T) or Reference product (R) will be administered to study subjects in sitting posture at fixed time with 240 mL ± 2mL of waterin each period. The order of receiving test and reference products will be as per randomization schedule. This activity will be followed by mouth and hand, check of the subjects to assess compliance to dosing.
Postural restrictions	**:**	Subjects will remain in upright position for 04 hours after dosing. During this period, subjects will be seated and may be permitted to walk in an upright position for natural exigencies and study procedures such as blood sampling and vital parameter measurements.
Clinical confinement	**:**	From at least 12.00 hours prior to drug administration and until 24.00 hours post dosing.
Total Study Duration	**:**	Minimum 69 days
Safety assessment	**:**	Vital signs measurement and subject wellbeing assessment will be done during subject check-in, housing, prior to checkout, ambulatory and post study.
Laboratory assessments	**:**	**Screening** – Hematology, Biochemistry, Serology, Urine analysis, ECG and serum pregnancy test (for females) **Check-In:** Alcohol breath analysis, urine drugs of abuse and urine

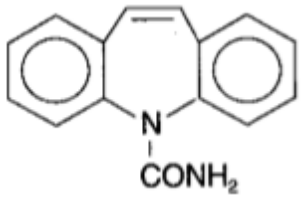
<table>
<tr><td>Sampling Schedule in each period</td><td>:</td><td>00.00 hour (Predose), 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.33, 03.67, 04.00, 04.33, 04.67, 05.00, 05.33, 05.67, 06.00, 07.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours post dose (Total of 25 samples - 03 mL each). First 22 samples will be collected in clinic and remaining samples will be collected as ambulatory.</td></tr>
<tr><td>Total amount of blood draw</td><td>:</td><td>The total volume of blood draw from each subject during the study will not exceed 358 mL.
<table>
<tr><td rowspan="2">Screening</td><td colspan="4">Pharmacokinetic Analysis</td><td rowspan="2">Discarded blood</td><td rowspan="2">Post study</td></tr>
<tr><td>Period I</td><td>Period II</td><td>Period III</td><td>Period IV</td></tr>
<tr><td>10 mL</td><td>75 mL</td><td>75 mL</td><td>75 mL</td><td>75 mL</td><td>42 mL</td><td>06 mL</td></tr>
</table></td></tr>
<tr><td>Analytes</td><td>:</td><td>Carbamazepine in plasma</td></tr>
<tr><td>Bioanalytical procedure</td><td>:</td><td>A validated LC-MS/MS bio-analytical method will be used for estimation of plasma levels of Carbamazepine.</td></tr>
<tr><td>Pharmacokinetic analysis and parameters</td><td>:</td><td>Pharmacokinetic analysis will be done using Phoenix®WinNonlin v 8.1.
Primary PK parameters: C_{max} and AUC_{0-72}
Secondary PK parameters: T_{max}</td></tr>
<tr><td>Statistical analysis</td><td>:</td><td>Statistical analysis will be performed on the pharmacokinetic parameters using SAS® v 9.4.</td></tr>
<tr><td>Bioequivalence criteria</td><td>:</td><td>In case SWR is less than 0.294
To establish bioequivalence of the test product with that of reference product, 90% Confidence Interval (CI) for the ratio (Test/Reference) of Least Square Means of the respective Ln transformed PK parameters (C_{max} and AUC_{0-72}) must fall between 80.00% - 125.00%.
Confidence Interval (CI) values should not be rounded off.
Therefore, to pass a CI limit of 80-125, the value should be at least 80.00 and not more than 125.00.</td></tr>
</table>

		In case SWR is equal to or more than 0.294 (In reference scaled average bioequivalence) The 95% upper confidence bound for $(\mu T - \mu R)\ 2 - \theta S2WR$ must be ≤ 0, $\theta = (\ln 1.25)2/\sigma 2w0$ (scaled average BE limit) and $\sigma w0=0.25$(Regulatory limit) and the point estimate of the Test/Reference geometric mean ratio must fall within 0.80 to 1.25 for respective Ln transformed PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) to establish bioequivalence of the test product with that of reference product.

5. Background Information

5.1 Description

Carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, XR tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5 mL (teaspoon). Its chemical name is 5*H*-dibenz[*b,f*]azepine-5-carboxamide, and its structural formula is:



5.2 Clinical Pharmacology

Pharmacodynamic

Mechanism of Action

GABA is an inhibitory neurotransmitter that plays an important role in regulating dopamine and glutamate neurotransmission**.** Carbamazepine is a GABA receptor agonist, as it potentiate GABA receptors made up of α1, β2, and γ2 subunits.Carbamazepine are associated with up regulation of $GABA_B$ receptors in the hippocampus, as a potential convergent mechanism for mood stabilization.Carbamazepine could exert anti glutamatergic effects both by decreased release of glutamate as well as by relative decreases in glutamate's postsynaptic efficacy by inhibiting calcium influx. Whereas reduction of glutamate release and stabilization of neuronal membranes may account mainly for the antiepileptic effects.Carbamazepine reduced D_2 receptor density and D_2-like receptor phosphorylation. Carbamazepine does decrease levels of the dopamine metabolite homovanillic acid (HVA) in the CSF.Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses.Carbamazepine inhibits sustained repetitive firing by blocking use-dependent sodium channels Pain relief is believed to be associated with blockade of synaptic transmission in the trigeminal nucleus and seizure control with reduction of post-tetanic potentiation of synaptic transmission in the spinal cord.

Pharmacokinetics

Absorption

Carbamazepine yield mean peak plasma concentrations of 4 to 5 hours after administration of conventional tablets. The bioavailability of Tegretol in various oral formulations has been shown to lie between 85-100%. Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of Tegretol. Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

Distribution

Carbamazepine in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5 to 25 mcg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 mcg/mL. The Cerebrospinal fluid/serum ratio is 0.22, similar to the 24% unbound Tegretol in serum. Because Tegretol induces its own metabolism, the half-life is also variable. Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels. Carbamazepine crosses the placental barrier. The apparent volume of distribution ranges from 0.8 to 1.9 L/kg.

Metabolism

Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10, 11-epoxide from carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10, 11-transdiol derivative from carbamazepine-10, 11 epoxide. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After oral administration of 14 C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces.

Excretion

Initial half-life values range from 25 to 65 hours, decreasing to 12 to 17 hours on repeated doses. Due to its own metabolism, the half-life is also variable. The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol.

5.3 Undesirable effects/Adverse effects

The most severe adverse reactions have been observed in the hemopoietic system, the skin, liver, and the cardiovascular system. The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting.

Hemopoietic System	Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, anemia, acute intermittent porphyria, variegate porphyria, porphyria cutaneatarda.
Skin	Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) , Stevens-Johnson syndrome , photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis.
Cardiovascular System	Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism (e.g., pulmonary embolism), and adenopathy or lymphadenopathy.
Liver	Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis; very rare cases of hepatic failure.
Pancreatic	Pancreatitis.

Respiratory System	Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.
Genitourinary System	Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated Blood Urea Nitrogen level(BUN) level, and microscopic deposits in the urine have also been reported. There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.
Nervous System	Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, hyperacusis, neuroleptic malignant syndrome. There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency. Isolated cases of neuroleptic malignant syndrome have been reported both with and without concomitant use of psychotropic drugs.
Digestive System	Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.
Eyes	Scattered punctate cortical lens opacities, increased intraocular pressure as well as conjunctivitis.
Musculoskeletal System	Aching joints and muscles, and leg cramps.
Metabolism	Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome, cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, decreased levels of plasma calcium leading to osteoporosis

Others	Multi-organ hypersensitivity reactions. Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides. A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications.

5.4 Indications

Carbamazepine is indicated for use as an anticonvulsant drug.

- Epilepsy, mania/bipolar disorder, and neuropathic pain
- Potentially be used by patients at high risk of Carbamazepine is associated with Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
- Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
- Generalized tonic-clonic seizures (grand mal).
- Mixed seizure patterns which include the above, or other partial or generalized seizures. It is usually not effective in absences (petit mal) and myoclonic seizure.

Trigeminal Neuralgia

- Carbamazepine is indicated in the treatment of the pain associated with true trigeminal neuralgia.
- Beneficial results have also been reported in glossopharyngeal neuralgia.
- This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

The posology and method of administration, warnings, precautions, contraindications and other details are provided in the Annexure II.

Carbamazepine is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between the effective carbamazepine concentrations and the concentrations associated with serious toxicity is narrow.
- Sub-optimal doses or concentrations lead to therapeutic failure or severe toxicity.
- Carbamazepine is subject to therapeutic monitoring based on pharmacokinetics measures.
- Carbamazepine has low-to-moderate within-subject variability.

Study Objective and Purpose

Primary Objective: To assess the bioequivalence between the test and reference formulations.

Secondary Objective: To monitor the safety and tolerability of the drug.

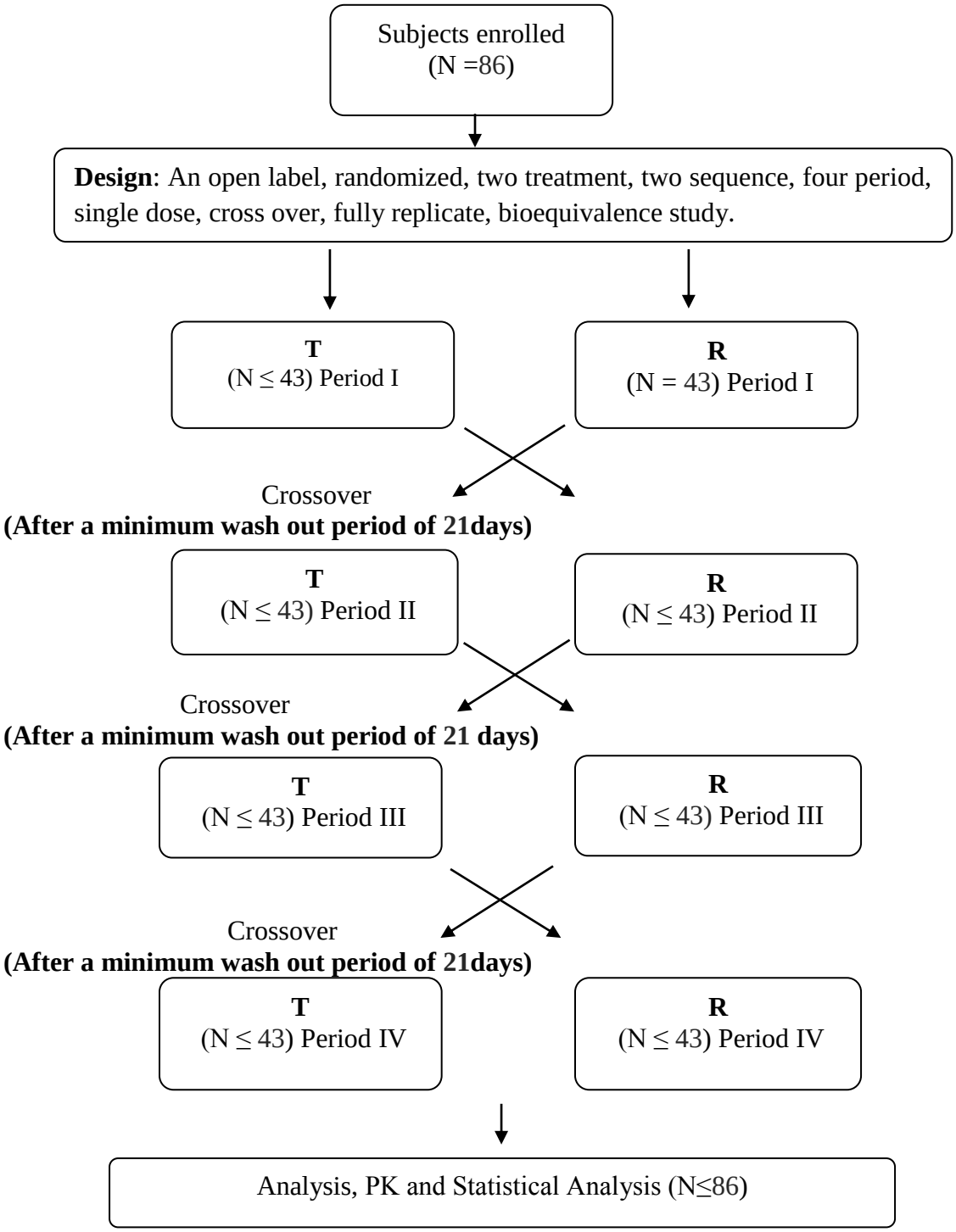
6. Study design

An open label, randomized, two treatment, two sequence, four period, single dose, crossover, fully replicate, bioequivalence study.

Primary PK parameters: C_{max} and AUC_{0-72}

Secondary PK parameters: T_{max}

6.1 Schematic diagram of study design



6.2 Randomization

Study subjects will receive any one of the investigational product in each period as per the randomization schedule. The randomization schedule will be generated by using SAS®. Each study subject will be randomly assigned to one of the following dosing sequences.

	Period I	Period II	Period III	Period IV
Sequence I	T	R	T	R
Sequence II	R	T	R	T

6.3 Blinding

The bio-analysts performing the bio-analysis will be kept blinded for the randomization and the randomization schedule will be made available only at the time of pharmacokinetic and statistical analysis.

6.4 Treatment to be evaluated

Study Treatments	
Test (T)	**Reference (R)**
Carbamazepine 200mg Tablets (Manufacturer detail is Confidential)	Tegretol (Carbamazepine) 200mg, Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936.

The batch number, manufactured date and expiry date of the investigational products will be provided in the study report.

6.5 Receipt, Storage, Labeling, Dispensing and Accountability of Investigational Products

The Sponsor will be supplying adequate quantities of investigational products, for the purpose of dosing and sample retention. The investigational products will be stored at the recommended temperature and conditions as per the product specifications.

Principal Investigator is overall responsible for Investigational product management. Ensure that Accountability of the Investigational products be performed after the protocol approval from Ethics Committee (EC).

Line clearance is the permission taken from the authorized personnel before starting the activities of Accountability, Dispensing and Retention. Accountability shall be performed for both test and reference in tandem.

Match the relevant information of the COA, Container/Strips Label, covering letter and protocol for complete information (like name of the investigational product, lot/batch number, manufactured by, manufacturing date, expiry/retest date, name of the manufacturer, storage condition against COA/Container/Strips label potency and assay value) and documented in Investigational Product Accountability form.

Carefully open one container/strips and check the physical appearance of the investigational product. Place the Physical Verification Unit in a separate High Density Polyethylene container/zip lock pouch and label it. Ensure that the investigational products are adequate to conduct the study and for retention, as per applicable regulatory requirements. Ensure that the accountability form is verified by QAU and Investigator.

If there is any discrepancy, inform to sponsor via e-mail through project management/designee. Complete the above activity and documented in Clinical Supplies Acknowledgement Form. Send a copy of the completed clinical supplies acknowledgement form to the sponsor through project management/designee.

The remaining investigational products will be retained for 05 years after completion of the bioequivalence study or one year after expiry of the investigational products whichever is later.

7. Selection and Withdrawal of Subjects

7.1 Inclusion Criteria

Volunteer will be enrolled into the study, who is meeting all the inclusion criteria as mentioned below:

- Nonsmoking, Healthy males and/or non-pregnant, non-lactating female literate volunteers of 20 to 45 years (both years inclusive) with BMI of 18.50 – 24.99 Kg/m^2 for males and females.
- Healthy volunteers as evaluated by medical history, vitals and general clinical examination.
- Normal or clinically insignificant biochemical, hematological, urine and serology parameters

- Normal or clinically insignificant ECG and chest X-ray
- Negative urine test for drugs of abuse, alcohol breath analysis for both males and females and negative pregnancy tests for females.
- Subjects who are willing to practice acceptable methods of contraception.
- Volunteers who can give written informed consent form and communicate effectively.

7.2 Exclusion Criteria

Volunteer will not be enrolled into the study who is meeting any of the exclusion criteria as mentioned below:

- History of any major surgical procedure in the past 3 months.
- History of any clinically significant cardiac, gastrointestinal, respiratory, hepatic, renal, endocrine, neurological, metabolic, psychiatric, hematological diseases.
- Subject who consumed tobacco containing products within 48 hours prior to proposed time of dosing.
- History of chronic alcoholism/chronic smoking/drug of abuse/ hypersensitivity.
- Present or past history of intake of drugs or any prescription drug or over the counter (OTC) drugs within 14 days which potentially modify kinetics / dynamics of Carbamazepine or any other medication judged to be clinically significant by the investigator.
- Consumption of grapefruit and/or its products within 10 days prior to the start of study.
- Subject who had participated in any other clinical study or who had bled during the last 3 months.
- Subjects who consume any xanthine containing food or drinks, citrus fruits and allied food (lime, lemon, orange and pomelo), alcoholic beverages and carbonated drinks such as cola during the stay in clinic and within 24 hours prior to dosing.
- Positive test for HIV testing, Hepatitis B and C.

7.3 Withdrawal criteria

Subjects will be withdrawn from the study for any of the following reasons. In case of withdrawal, the details will be documented in the appropriate Case Report Form (CRF).

- The subject withdraws consent.
- Development of an intolerable adverse event or other reasons of safety.

- Significant non-compliance to protocol and study procedures as deemed by the Principal Investigator.
- Subjects who require administration of medicines as a part of medical management that are known to interfere with the pharmacokinetics of study drug

Withdrawn subjects will not be replaced.

8. Treatment of subjects

8.1 Housing

Subjects will be housed in the Clinical Pharmacology (CPG) Unit of Amaris Clinical. They will be checked in at least 12 hours before the proposed time of drug administration in each period of the study (tentatively dosing will start from 08.30) until 24 hours post dose.

8.2 Diet and Water

After check-in (Day 0), subjects will receive standard dinner after which they will be required to fast overnight for at least 08.00 hours before dosing. Being a fasting study, subjects will not be served breakfast on the day of dosing. The subjects will receive standard food approximately at 04.00, 08.00and 12.00 hours post-dose with time flexibility of +15 minutes.

Drinking water will not be permitted 01 hour before dosing and until 01 hour post-dose, at all other times drinking water will be permitted ad libitum.

Subjects will not be provided coffee, tea or any other xanthine containing food or drinks and carbonated drinks during the stay in clinic. They will be instructed not to consume grapefruit containing juice / food items or food items containing citrus fruits (lime, lemon, orange and pomelo) and alcohol and during the entire period of study.

8.3 Postural and physical activity restrictions

Subjects will be administered with study medications in sitting posture. Subjects will remain in an upright position for at least 04 hours after dosing, when the subjects will be seated and may be allowed to walk for short intervals, for any natural exigencies or study related activities such as blood sampling and vital parameters measurement. No exercise or strenuous physical activities are permitted during the clinic stay. If the postural restriction is not followed for any reason except due to an adverse event(s) and its management, the same will be considered a protocol deviation.

8.4 Dispensing

On previous working day of dosing in each period, the dispensing will be done by the pharmacist in the presence of Quality Assurance personnel as per the randomization schedule. The dispensed products will be retained in the pharmacy till dosing.

8.5 Dosing

A single oral dose of test (T) or Reference product (R) will be administered to study subjects in sitting posture at fixed time with 240mL ±2mL of water in each period. The order of receiving test and reference products will be as per randomization schedule. This activity will be followed by a mouth and hand check to assess compliance to dosing.

8.6 Sampling Schedule

00.00 hour (Predose), 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.33, 03.67, 04.00, 04.33, 04.67, 05.00, 05.33, 05.67, 06.00, 07.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours post dose (Total of 25 samples – 03 mL each). First 22 samples will be collected in clinic and remaining samples will be collected as ambulatory.

8.7 Sampling Procedure

Sample Handling and Processing

First 21 blood samples in each period will be collected through an indwelling cannula placed in a forearm / arm vein remaining samples will be collected through direct venous puncture. All the samples will be collected using pre-labeled vacutainers containing K_2EDTA at the scheduled times.

After insertion of intravenous cannula and whenever blood is drawn from intravenous cannula, 0.5 mL of heparinized saline will be injected to prevent the cannula blockade. If there is difficulty in obtaining blood sample through intravenous cannula, blood sample will be obtained by direct venous puncture.

The pre-dose samples will be collected within 02 hours prior to drug dosing.

The post-dose samples will be collected within 02 minutes of the scheduled time where the end time of collection to the nearest minute would be recorded. Any deviations beyond two minutes would be recorded as Protocol deviation.

Blood samples collected during the study will be centrifuged at 4000 rpm for 10minutes 4 ± 2°C. Plasma will be separated into 02 aliquots and stored at about -70°C or colder till analysis. First aliquot will have 01 mL of plasma and remaining plasma in the second aliquot.

8.8 Total Blood Withdrawn

The total volume of blood draw from each subject during the study will not exceed 358 mL.

Screening	Pharmacokinetic Analysis				Discarded blood	Post study	Total blood loss
	Period I	Period II	Period III	Period IV			
10 mL	75 mL	75 mL	75 mL	75 mL	42 mL	06 mL	358 mL

8.9 Sample transfer procedures

The plasma samples will be segregated subject wise and retrieval of samples will be performed using SAM HD. Dispatch the retrieved study sample to Bio analytical department through access window which is documented in the sample request form.

If the samples are to be sent to sponsor/outside laboratory, it should be packed in zip lock cover and dispatch through courier with the thermometer or data logger.The details of the temperature and time of keeping the samplesand other relevant details should be entered in "Transfer of clinical samples".The Transfer of clinical samples should retained in the Trial Master File.

The sample transfer process is briefed below:

- The samples will be segregated subject wise
- The segregated samples will be packed in the zip lock covers with labels
- All the samples will be transferred using a thermo insulated box containing dry ice/ ice pack and a thermo probe and/ or data logger

The temperature of the thermo insulated box will be monitored for consistency.

9. Assessment of Safety

9.1 Assessment of Vital signs and Subject wellbeing

Pulse rate, Blood pressure and subjects well-being will be recorded during check in, at 00.00 (pre dose),02.00, 08.00 and 12.00 hours post-dose in each period, prior to check-out, during ambulatory, post study and at discretion of clinical staff. Temperature will be recorded during check in, prior to

check out and post study. 00.00 hour vitals can be recorded within two hours prior to drug administration. If 00.00 hours vitals are found to be abnormal and clinically significant, subject will be withdrawn from the study. Vital parameters at other time will be recorded with the time flexibility of ±30 minutes. During ambulatory visits, the vital parameters will be recorded at the actual time of visit, before blood sampling.

Whenever necessary, vital parameters will be measured at any time point to ensure safety of the subjects.

Screening Laboratory Tests:

Biochemistry: Glucose random blood sugar, Urea, Creatinine, Total cholesterol, Bilirubin (total), Bilirubin (direct), Bilirubin (indirect), Alanine aminotransferase (SGPT), Aspartate aminotransferase (SGOT), Alkaline phosphatase, Protein, Albumin, Globulin, Albumin/Globulin ratio, Lactate dehydrogenase, Gamma Glutamyl Transferase (GGT), Sodium, Potassium, Chloride and Calcium.

Hematology: Erythrocytes, Leukocytes, Differential leukocyte count, Hemoglobin, Hematocrit (PCV), Platelets count.

Urine: Appearance, Colour, Bilirubin, Urobilinogen, Ketone, Protein, Nitrite, Glucose, pH, Specific Gravity, Microscopic Examination (Erythrocytes, Leucocytes & Epithelial cells).

Serology: HIV 1 & 2, Hepatitis B surface antigen, Hepatitis C antibody, Rapid plasma reagin.

Others: ECG, Chest X-ray and Serum pregnancy test (for females).

Check In Laboratory tests:

- Urine drugs of abuse such as cocaine, amphetamine, tetra hydro cannabinoid, benzodiazepine, barbiturate and opioid
- Alcohol breath analysis
- Urine pregnancy test for female volunteers

9.2 Handling and reporting of AE and SAE

9.2.1 Definition of AE

An adverse event is “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment”.

9.2.2 Definition of SAE

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Results in a congenital anomaly/birth defect
- Others (medically significant, requiring intervention)

The term "life threatening" in the definition of SAE refers to an event in which the patient / subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

9.2.3 Monitoring and Recording of AE and SAE

If any Adverse Event (AE) or Serious Adverse Event (SAE) occurs during the study, the event will be recorded in the AE or SAE recording forms. A complete description of the event, severity of the event, Causality relationship between the study drug & the event and details of the study drug and concomitant medication will be entered in the AE / SAE recording forms. The causality between the study drug and the event will be assessed as given below.

9.2.4 Evaluation of AE and SAE

Relationship to study drugs

During clinical study, if the subject informs as'unwell' or experiences any adverse effect or any abnormal values found during vital sign monitoring, it should be brought to the notice of the PI/ CI/ Physician. Attend the subject immediately and diagnose the event.

Record the signs and symptoms of the AE/ SAE, time and date of onset of the AE/SAE, the time and date when the AE/ SAE is reported, the method of reporting and the severity of the AE / SAE in the form, 'Adverse Event Recording Form' / ' Serious Adverse Event Recording Form'.

Record the action taken and final outcome. Classify the relationship/causality of the adverse event to the study drug according to the WHO-UMC system for standardised case causality assessment.

If subject becomes pregnant during IP administration (After period I dosing and before completion of study), treatment shall generally be discontinued if this can be done safely, Follow up evaluation of Pregnancy, Foetus, child and details of abortion if any are important and the same shall be documented.

SAE reports to licensing authority shall be in colour coded binding, SAE's of death in red cover, SAE's of injury other than deaths in blue cover and remaining cases of SAE's in white cover.

Grading of AE

The adverse events will be graded as mild, moderate or severe as per standard operating procedure.

9.2.5 Reporting of AE and SAE

Investigator shall report all serious adverse events to the licensing authority, the sponsor and ethics committee within 24 hours of the occurrence of the event.

The report, of the serious adverse event, after the analysis shall be forwarded to the Licensing Authority, Chairman of the Ethics Committee within 14 days of occurrence of the serious adverse event.The report of SAE of death in addition, also shall be forwarded to the chairman of expert committee appointed by Licensing Authority.

In case of serious adverse event, occurring to the clinical study subject, the Ethics Committee shall forward its report on the serious adverse event after the analysis along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, to the Licensing Authority within 30 days of the occurrence of the serious adverse event.

9.2.6 Follow up of AE and SAE

All AEs and SAEs will be followed to the availability of the study participant by the investigator proactively till resolution. The investigator will ensure that follow up includes any supplemental investigations as may be indicated to elucidate the nature and / or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.

Document the AE follow up details in 'Adverse Event follow up form'. If the subject is not returned back for post study follow-up up to six months, classify the outcome as "Not Known" and consider the subject as "Lost to follow up". Ensure that all telephonic communication made between CRO and the subject is recorded in Adverse Event follow up form'.

Unable to follow up – A volunteer will be declared as "Unable to follow up" following failure of all attempts to contact the volunteer.

Also apart from initial AE / SAE report, follow up information will be made available to the sponsor, ethics committee and licensing authority, as applicable.

9.2.7 Clinical laboratory evaluations

During the evaluation of screening laboratory results or post study lab data, if any abnormal borderline deviations are encountered, the investigator will correlate with the other related lab parameters, clinical findings and examination to decide whether the out of range values are clinically significant or not.

9.3 Handling of emergencies

Carbamazepine are being used safely in the clinical practice and hence in this study no life threatening adverse event is expected to happen. Furthermore, the ICU will be used to deal with the unexpected life threatening AEs as necessary. A fully equipped ambulance will be kept available during the study.

9.4 Post study safety evaluation

Physical examination, vital parameter assessment and wellbeing assessment will be performed to all study subjects during subject check-out, in each period, to ensure safety of the study subjects. Post study safety assessments will be performed for all the subjects. For subjects who are discontinued from the study following administration of at least one dose of either test or reference product, the post study safety assessment will be done prior to check out based on the willingness of the subject to give blood for post study safety assessment. If a subject does not report for the subsequent periods, he/she will be followed up for the safety assessment. Investigators may also follow up with subjects after the study, in cases of out of range lab values, potential medical problems and other reasons, with discretion, in the interest of subject safety.

Post study Laboratory tests:

Biochemistry: Glucose random, Urea, Creatinine, Total cholesterol, Bilirubin (total), Bilirubin (direct), Bilirubin (indirect), Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase, Protein, Albumin, Globulin, Albumin/Globulin ratio, Lactate dehydrogenase, Gamma Glutamyl Transferase, Sodium, Potassium, Chloride and Calcium.

Hematology: Erythrocytes, Leukocytes, Differential leukocyte count, Hemoglobin, Hematocrit (PCV), Platelets count.

Urine analysis: Appearance, Colour, Bilirubin, Urobilinogen, Ketone, Protein, Nitrite, Glucose, pH, Specific Gravity, Microscopic Examination (Erythrocytes, Leucocytes & Epithelial cells)

Others: Serum pregnancy test (for female volunteers).

9.5 Bioanalytical Methodology

- Validated LC-MS/MS methods will be used for estimation of Carbamazepine in plasma.
- Bio-analytical method validation will be done as per FDA's Bio-analytical Method Validation guidance, with evaluation for Specificity, Sensitivity, Precision and Accuracy, Stability, Recovery and Dilution Integrity. Subject samples will be analyzed using these validated methods.
- Incurred Sample Reanalysis (ISR) is the repeated measurement of an analyte's concentration from study samples to demonstrate reproducibility. Research Associate will perform ISR to verify the reliability of the reported study sample analyte concentrations. ISR samples may be selected individually for multiple analyte(s) or metabolites and document it in Authorization for Incurred Sample Reanalysis.
- Perform ISR in separate analytical run and report the ISR results and document in Result of Incurred Sample Reanalysis. Use Bulk Frozen Calibration Standards and Quality Control samples for ISR analysis. Calculate the % difference between the Original value and ISR value and it should be within ±20%.
- In case 675 of the analysed ISR samples did not meet the acceptance criteria, initiate the investigation after assessing the reliability of the assay and method as in Investigation of Batch/Run Failure. ISR is approved by Head-Bioanalytical/Manager.
- Samples of subjects who complete the study will be considered for analysis.

9.6 Pharmacokinetic Analysis

The concentration values which are reported as BLQ will be set to "Zero" for all pharmacokinetic and statistical evaluation. The Pharmacokinetic parameters (AUC_{0-72},$C_{max}$and T_{max}) will be calculated using Non compartmental Model of Phoenix® Win Nonlin v 8.1.

PK Parameters:

C_{max}	:	Maximum plasma concentration
AUC_{0-72h}	:	Area under the plasma concentration curve from administration to 72h
T_{max}	:	Time until Cmax is reached

Primary PK parameters: C_{max} and AUC_{0-72}

Secondary PK parameters: T_{max}

For the Pharmacokinetic analysis, if there are blood sampling/protocol deviations, the actual time of blood collection will be used.

9.7 Criteria for exclusion of subjects from data analysis

- If the pre-dose concentration is more than 5% of C_{max} of the respective subject, then the subject will be dropped from bioequivalence analysis.
- Data from subjects who experiences vomiting within two times the median T_{max} will be excluded from statistical analysis.

9.8 Statistical Analysis

Statistical analysis will be performed on the Ln-transformed pharmacokinetic parameters using SAS® v 9.4. The analysis will include data from subjects who complete all the periods of the study. If there are drop outs, no replacement will be done.

9.8.1 Exploratory Data Analysis

9.8.2 Descriptive analysis

Descriptive analysis of plasma concentration (time point wise and formulation wise) and pharmacokinetic parameters – $C_{max,}AUC_{0-72}$andT_{max} will be reported for test and reference products. The reported parameters will be the mean, minimum, maximum, range, standard deviation, Standard error, geometric mean and the coefficient of variation.

9.8.3 Analysis of Variance (ANOVA)

The log-transformed pharmacokinetic parameters (C_{max} and AUC_{0-72}) will be analyzed using ANOVA Model with the main effects of treatment, period, group (if applicable) and sequence as fixed effects and subjects nested within sequence as random effect. A separate ANOVA model will be used to analyse each of the parameters. The sequence effect will be tested at the 0.10 level of significance using the subjects nested within sequence mean square from the ANOVA as the error term. All other main effects will be tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term.

9.8.4 Two one sided t tests

Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals for the difference between the test (T) and reference (R) means will be calculated for the log transformed data.

9.8.5 90% Confidence Intervals

The confidence limits are expressed as a percentage of the least square mean (LSM) of the reference formulation. Using the confidence limits of the above confidence interval and the LSM of the reference product, 90 % confidence interval for the ratio of the test and reference product means will be calculated.

9.8.6 Ratio analysis

The log transformed primary PK parameters (C_{max} and AUC_{0-72}) will be subjected to ratio analysis. The Test / Reference ratio will be calculated for log transformed primary PK parameters.

9.8.7 Bioequivalence Criteria

In case SWR is less than 0.294

To establish bioequivalence of the test product with that of reference product, 90% Confidence Interval (CI) for the ratio (Test/Reference) of Least Square Means of the respective Ln transformed PK parameters (C_{max} and AUC_{0-72}) must fall between 80.00% - 125.00%.

Confidence Interval (CI) values should not be rounded off.

Therefore, to pass a CI limit of 80-125, the value should be at least 80.00 and not more than 125.00.

In case SWR is equal to or more than 0.294 (In reference scaled average bioequivalence)

The 95% upper confidence bound for $(\mu T - \mu R)\ 2 - \theta S2WR$ must be ≤ 0, $\theta = (\ln 1.25)2/\sigma 2w0$ (scaled average BE limit) and $\sigma w0=0.25$(Regulatory limit) and the point estimate of the Test/Reference geometric mean ratio must fall within 0.80 to 1.25 for respective Ln transformed PK parameters (C_{max} and AUC_{0-72}) to establish bioequivalence of the test product with that of reference product.

9.8.8 Justification for the sample size

For an expected mean difference of 5% between the formulations, with intra-subject CV of 12 %, 43 subjects would be required to prove bioequivalence at 90% power. On the basis of Cross over design and considering possible dropouts due to expected adverse drug reaction (ADR) a sample size of 86 subjects is suggested for pivotal bioequivalence study.

9.8.9 Demographics and Baseline Characteristics

Frequency distributions of age, gender and race will be tabulated.

10. Data Management

10.1 Documentation

Entire data generated during the conduct of the study will be directly recorded in raw data forms. The source data for the lab report will be retained by the clinical laboratory. Raw data will be completed by the study personnel and checked by the respective and designated personnel wherever applicable. All data related to the project will be in the custody of the Principal Investigator until transferred to archives.

10.2 Accessibility

All data generated during the conduct of the study will be kept confidential and will be accessible only to concerned regulatory authority, sponsor, ethics committee and designated personnel of Amaris Clinical.

10.3 Financing and Insurance

Amaris Clinical has an agreement with <XXX> for the insurance coverage of the volunteers participating in the study. Situations that require unplanned financial compensations may be covered by the same.

10.4 Supplementary documentation

The final report will include a sample of the protocol, informed consent form along with the translated copies, a copy of ethics committee approval, randomization, vital monitoring, wellbeing assessment, AE/SAE recording forms and sample collection records. The final report will be in the e-CTD format.

10.5 Study termination

The study may be terminated

- If a data not known before starting the study become available and raises concerns about the safety.
- Due to medical reasons that can lead to intolerable adverse events.

The details of the termination will be informed to the study sponsor and ethics committee.

10.6 Quality Assurance audits

All raw data and reports generated during the course of the study will be liable for inspection and quality audit for conformance to this protocol and all the governing standard operating procedures of Amaris Clinical and applicable regulatory guidelines by the quality assurance unit. An audit schedule will be drawn prior to the study, audit reports will be made and audit certification will be issued after the audit of the reports.

10.7 Data Handling and Record Keeping

Electronic copies (if generated) or else the paper copies of the entire raw data (including forms filled in the clinical section, medical screening records, Chest X-ray, ECG reports & pathology reports and chromatograms & bio-analytical data) generated during the study along with a copy of the protocol, informed consent forms and its amendments, ethics committee correspondence and recruitment advertisements (if any) will be archived. Archival will be for a minimum period of 05 years or as per the applicable regulatory requirements.

10.8 Ethics

Approval of the study protocol and informed consent documents will be obtained from the Ethics Committee (EC). Details (XXX)

10.9 Publication policy

Publication of the results of the study shall be at the discretion of the sponsor and Amaris Clinical shall not publish any data without the prior consent of the sponsor.

11. List of annexure

1. Annexure I – Template For Study Specific InformedConsent Form
2. Annexure II – Prescribing Information of Tegretol (Carbamazepine) 200mg Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936.
3. Annexure III- Template For Case Report Form

12. Protocol Approval

The protocol should comply with all the other pertinent requirements of "Applicable US FDA guidance documents & 21 CFR parts", "ICH Guidelines for Good Clinical Practices E6 (R2) 2016", "Schedule Y of Drugs and Cosmetics Act, 20th January 2005 and its amendments", "Good Clinical Practices for Clinical Research in India", "CDSCO Guidelines for BA/BE Studies, March 2005", the principles enunciated as per the Declaration of Helsinki and in compliance with Good Laboratory Practice.

XXX,
Principal Investigator, Amaris Clinical
(Signature)

XXX,
Bio-analytical Investigator, Amaris Clinical
(Signature)

XXX,
Sr. Statistician, Amaris Clinical
(Signature)

ANNEXURE I

TEMPLATE FOR STUDY

SPECIFIC INFORMED CONSENT FORM

Informed Consent Form

Information sheet

Registration number: _____ Date: _____

Study title
An open label, randomized, two treatment, two sequence, four period, single dose, crossover, fully replicate, bioequivalence study of Carbamazepine 200mg Tablets (Manufacturer detail is confidential) and Tegretol (Carbamazepine) 200mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936.

Dear Prospective Subject,

You are invited to participate in a bioequivalence study, the title of which is given above. The purpose of this informed consent document is to clearly state the procedures of the study and to ensure that you enter the study only after knowing all relevant facts about it. An oral presentation of this document will be made after you go through this Informed Consent document. Only if you have understood all the salient aspects of the study procedures and decide to take part in this study, you will be asked to sign this Informed Consent Form to confirm your voluntary participation in the study. A photocopy of the signed informed consent form will be given to you for your reference.

Nature and purpose of this study

You are being invited to participate in a bioequivalence study on drug called Carbamazepine. This study compares test product, Carbamazepine 200mg (Manufacturer detail is confidential) and Tegretol (Carbamazepine) 200mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936, in XX healthy, adult, human subjects under fasting conditions whether these drugs achieve similar blood concentrations or not.

Carbamazepine 200mg (Manufacturer detail is confidential) of "Test product" (T) and the formulation of Tegretol (Carbamazepine) 200mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 of "Reference product" (R) which is already available in the market worldwide. In a random order, you will receive the reference drug in two periods and the test drug in other two periods during your participation in this study.

The drug(s) under investigation is not given to you to treat any disease nor is intended to improve your health status, but is given to you for the purpose of research.

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Drug information

Carbamazepine is used to prevent and control seizures. This medication is known as an anticonvulsant or anti-epileptic drug. It is also used to relieve certain types of nerve pain (such as trigeminal neuralgia). This medication works by reducing the spread of seizure activity in the brain and restoring the normal balance of nerve activity.

The most severe adverse reactions have been observed in the blood, the skin, liver, and the heart.

Common Side Effects of Tegretol:

- Dizziness
- Drowsiness
- Problems with walking and coordination
- Nausea
- Vomiting

Serious Side Effects of Tegretol:

- Irregular heartbeat
- Shortness of breath
- Fainting or feeling lightheaded
- Liver problems(yellowing of the skin or whites of eyes, dark urine, pain on the right side of your stomach, easy bruising, loss of appetite)

Rare but serious skin rash:

- Skin rash
- Sores in your mouth
- Blistering or peeling of the skin

Rare but serious blood problems:

- Fever
- Sore throat
- Easy bruising
- Red or purple spots on your body
- Bleeding gums

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- Nose bleeds
- Severe fractures
- Weakness

Suicidal thoughts or actions:

- Thoughts about suicide or dying
- Attempts to commit suicide
- Thoughts of hurting yourself
- A new or deepening depression
- Severe anxiety
- Reckless behavior
- Unusual hyperactivity
- Panic attacks

Get emergency medical help if you have any signs of an allergic reaction, such as:

- Hives
- Difficulty breathing
- Swelling of the face, lips, tongue, or throat

All the above mentioned adverse events are observed during clinical trials, however participating in the clinical study may involve risks (including life-threatening situation) to the subject which are currently unforeseeable. If you require more information about other side effects, the same will be provided to you.

Total number of volunteers, number of visits and duration of study & stay

This study will be carried out in 86 healthy, adult, human male and /or non-pregnant female volunteers and it consists of 4 periods. After check-in, you need to stay in our clinic for 36 hours. If you check-in today evening, study drug will be administered tomorrow morning in sitting posture. After last drug administration, you have to stay for at least 24hours. You need to visit the clinic for ambulatory samples at 36.00, 48.00 and 72.00 hours post dose.

There will be a wash out period of at least 21days between each period. Hence the total duration of study will be minimum 69 days (from the day of Check-in of period I to post study assessment).

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Description of the Study Procedures

Only healthy male and /or non-pregnant female volunteers can participate in this study. To ensure that you are actually healthy, you have undergone a screening procedure and you are found to be eligible for the study. We obtained a similar consent from you for screening also. Today we will test your breath for whether you have consumed alcohol and your urine for whether you have consumed any drugs of abuse such as cocaine, amphetamine, tetra hydro cannabinoid, benzodiazepine, barbiturate and opioid.

Your participation in the study will be based on your health status which will be decided based on the laboratory parameters and on the general examination done by the physician/ investigator. You will be subjected to check in process after physician/investigator confirms eligibility based on fitness.

Procedures after check-in

Once you give consent to participate in the study, you will be subjected to check-in procedure, during which you need to keep all your belongings including clothes in the locker allotted to you. You have to wear the clothes that we provide.

After subject check-in, dinner will be provided. You have to sleep in our clinical facility. You will be woken up around 05.00. You have to finish all your morning ablutions within 06.00, after which you will be inserted an intravenous cannula. The study drug will be administered tentatively at around 08.30. You need to stay at least 24 hours after drug administration.

A single oral dose of test (T) or Reference product (R) will be administered to you in sitting posture at fixed time in each period. The order of receiving test and reference products will be as per randomization schedule.

This activity will be followed by mouth and hand check to assess compliance to dosing.

In this study, the concentration of the drug in your blood will be measured by giving the study medication under fasting conditions. Being a fasting study, you will not be served breakfast on the day of dosing. Standard food will be served at all other times (approximately at 04.00, 08.00 and 12.00 hours post-dose with time flexibility of +15 minutes). During the entire stay in our facility, at scheduled times, blood samples will be taken from you, vital parameters will be recorded and your well-being will be assessed. The details of all these scheduled activities are given below. You will also be subjected to restrictions in the posture and activities which are dealt separately.

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Timings described in this document may vary depending on the check in time & time of dosing and subjects will be updated about the changes.

Study restrictions

You will be restricted from smoking, consuming alcohol, taking carbonated drinks, coffee, tea and other caffeine containing drinks or food. You will have to eat only the food that we provide during the study. You will not be provided any food or juice containing grapefruit or other citrus fruits. You are also instructed not to consume the restricted food and drinks during the entire period of study including wash out period.

Before dosing, you will be put in at least 10 hours of fasting. Water intake will be restricted one hour before drug administration and one hour after drug administration, except the 240mL of water given during the drug administration. Rest of the times water can be taken whenever you feel to take.

During the entire duration of the study, you are restricted from taking any other medication including the over the counter (OTC) drugs. If you take any such medications, please inform the study personnel. Because, there are drugs that may interact with the study medication & result in adverse effects and it is for your safety for you to reveal the true information, if you have taken any other medication.

After the ingestion of the study medication, you are required not to lie down for atleast 04 hours. So, you have to be in the sitting position for 04 hours after dosing. Throughout your stay in our clinical facility, you can enjoy the comfortable stay, but you are restricted from doing any strenuous activities.

Blood sample collection

In each period of the study, a total 25 blood samples will be collected. The sample time point schedule is as follows.

00.00 hour (Predose), 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.33, 03.67, 04.00, 04.33, 04.67, 05.00, 05.33, 05.67, 06.00, 07.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00 hours post dose (Total of 25 samples – 03 mL each).First 22 samples will be collected in clinic and remaining samples will be collected as ambulatory.

21blood samples in each period will be collected through an indwelling cannula placed in a forearm / arm vein remaining samples will be collected through direct venous puncture. After insertion of intravenous cannula and whenever blood is drawn from intravenous cannula, 0.5 mL of normal saline will be injected to prevent the cannula blockade. If there is difficulty in drawing blood from intravenous cannula due to blockade, blood will be

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drawn by direct venous puncture.

The total volume of blood draw from each subject during the study will not exceed 358mL.

Vital parameter and well-being assessment

In each period, vital parameters such as Pulse rate, Blood pressure and subject's well-being will be recorded during check in, at 00.00(pre dose) 02.00, 08.00and 12.00hours post-dose in each period, prior to check out, during ambulatory and at discretion of clinical staff. Temperature will be recorded during check in, prior to check out and post study. Your well-being will also be assessed by asking "Are you feeling ok/good?" during the vital parameter assessment.

Post Study Assessment

At the end of the study, the biochemical, hematological parameters and serum pregnancy test (for females) will be evaluated, to ensure that you are not having any abnormal laboratory parameters.

Risks or discomforts

The important foreseeable risk that you may face during the study is the possibility of an adverse event or side-effect which may or may not be related to the drug.

Apart from the adverse events, you may have to face the pain / discomfort of cannulation of the vein and repeated blood withdrawal and study restrictions as mentioned above.

Unforeseeable risks

Since this drug Carbamazepine is in the market for quite some years and all aspects of its efficacy & safety are well studied, there are no unforeseeable risks associated with it. However, an allergic reaction is always a possibility associated with the usage of any drug and if any such reaction happens, we are well prepared to deal with it.

Benefits to subjects/Society/Community

Since you are a healthy volunteer and you do not suffer from any disease, you will not have any direct benefits by taking the study medication. But society in general will benefit from these studies because these studies help in introducing many formulations of the same drug in the market. Thus these studies increase competition and ensure availability of drugs at more cost effective prices.

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Alternative procedures or any other treatments

No alternative procedures are available. If you don't want to take the drug, then you can refuse to participate.

Confidentiality of Records

It may become necessary for us to seek details from you about your health and personal details. Since this is mostly for your own safety, please do not hide any fact. All your personal details and your identity will be kept strictly confidential at Amaris Clinical. The details will be revealed only when demanded by Governmental Regulatory Authorities, Independent Ethics Committee or sponsor's inspectors / auditors.

Subject Safety

The study related documents such as the protocol, Informed Consent Document have been scrutinized by the Independent Ethics Committee (IEC) and have been approved.

In case of study related injury or death, sponsor/sponsor's representative or whosoever obtain the permission from the licensing authority, will provide complete medical care as well as compensation for the injury or death. Further in case of such injuries or deaths, the details of compensation provided will be intimated to Drug Controller General of India.

If any adverse event happens to you due to your participation in this study, the necessary medical assistance will be provided at Amaris by the investigator or at a nearby hospital for which we ourselves will directly bear the cost. We will provide no monetary benefit for you other than providing the necessary medical care in case of any adverse events.

Voluntary Nature of Participation

Please remember that your participation in this study is entirely voluntary and this document is presented to you to help you in making an informed decision. If you have any doubts regarding the study, you can ask questions to any of our study staff and clarify them to your utmost satisfaction.

Refusal to participate in this study will involve no penalty or loss of benefits, to which you might otherwise be entitled.

Subject withdrawal

You have the right to decide to participate or not to participate in the study. Even after giving consent, you have the right to withdraw from the study at any point of time without affecting your medical care.

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Termination of subject participation

At any point of time, your participation in the study may be terminated due to the following reasons, by the Principal Investigator even without your consent.

1. You withdraw the consent.
2. Development of intolerable adverse event due to study participation as determined by the investigator and / or yourself.
3. Discovery that you entered the trial in violation of the protocol or occurrence of a significant protocol violation during the study.
4. The investigator feels that in the best interest of your health, you have to be withdrawn from the trial.
5. Any misbehavior or misconduct with any study personnel or with any other fellow subject, on disciplinary grounds or if you are non-cooperative for the study conduct.

Even when you are terminated from participating in the study, if you require any medical care it will be provided.

Termination of the study

The study at any point of time can be terminated even without the consent or knowledge of the subject. But the same will be intimated to all the subjects for information. The study can be terminated for the following reasons.

1. The investigator and / or sponsor feel that the number and / or the severity of the adverse events justify the discontinuation of the study.
2. Data not known before become available and raise concern about the safety of the study drug so that continuation would pose potential risks to the subjects.
3. The Ethics Committee and / or regulatory authority may terminate the study, if continuation of study compromises subject safety.

When the study is terminated prematurely, if the study subjects need any medical care it will be provided.

Compensation to the subject

As per our compensation policy, for the time and effort that you put in this study, you will be paid Rs. _____/- (Rupees _____ only).

Amaris Clinical has an insurance policy to cover the medical expenses incurred during the management of

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adverse events that happen during the study. In case of study related injury or death, sponsor/sponsor's representative or whosoever obtain the permission from the licensing authority, will provide complete medical care as well as compensation for the injury or death. Further in case of such injuries or deaths, the details of compensation provided will be intimated to Drug Controller General of India.

You will be covered by contingency policy with insurance cover (The current policy is given by "United India Insurance Co. Ltd."). The risks covered for death and physical disability arising out of such clinical trial and also hospitalization expenses arising out of illness consequent to such trials and Accidental damage cover.

In case of death, the nominee will be eligible for compensation and all the trial related compensation will be paid to the nominee of the subject as per updated DCGI requirements.

The address to be contacted in case of study related injury or death.

Amaris Clinical
(A Division of Caplin Point Laboratories Ltd),
No 44, 8th Avenue, Domestic Tariff Area
Mahindra World City, Chengalpattu,
Tamil Nadu 603004.

In case of SAE, compensation amount will be decided by chairman of ethics committee which has to be approved by licensing authority or Independent expert committee, and sponsor/sponsor's representative or whosoever obtains the permission from the licensing authority, will provide that compensation for the injury or death. In case of study related injury or death, sponsor/sponsor's representative or whosoever obtain the permission from the licensing authority, will provide complete medical care as well as compensation for the injury or death. In case there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages.

Compensation for participation in the study will be paid to the volunteers proportionately at the end of each period of the study.

In case if your participation is terminated in the study due to medical reasons or if the study is terminated as per the sponsor's or investigator's decision, you will be paid the full compensation amount.

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But if your participation in the study is terminated because of your withdrawal of consent or due to disciplinary reasons, the compensation will be proportionate to the stage of your participation in the study.

Please note that the participation fee also includes your transportation to and from our facility. Hence no separate amount will be paid for transportation.

New findings

We have tried to provide you with the latest information regarding the drug and regarding bioequivalence studies. In case of any new information on the drug that might influence your decision to continue the study will be communicated to you and you may review your decision to continue your participation in the study based on such new information.

Others

In case of a serious adverse event, the physician has the authority to provide emergency medical care to ensure your well-being without regard to the provisions of this document.

When the adverse event is managed, at times, additional lab investigations including blood, urine, X ray, ECG and other necessary tests may be performed. By signing this form you also give consent to take any additional volume of blood required for further lab tests and for any other additional tests.

Key study contacts

For any questions about our location, how to get here, and what time to report, contact:

VM Manager,
Company Name,
Mobile No: XXXXXXXX.

If you have any questions about the study or the safety aspects or the study related injury and medical questions, contact:

Dr. XXX,
Principal Investigator,
Amaris Clinical.,
Mobile No: XXXXXXXXX

If you have any queries or clarifications about your rights in the study or about ethical aspects of the study, you

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can contact the IEC at this address.

XXXXX

Declaration by the volunteer	Initial in the box
i. I confirm that I have read and understood the information given above pages and have had the opportunity to ask questions and the study staff clarified them.	[ ]
ii. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
iii. I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
iv. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).	[ ]

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v. I understand that the volume of blood to be drawn from me will not exceed 358mL. However I understand that during the management of an adverse event, any additional amount of blood deemed to be necessary may be taken from me and I give consent for this and any other additional tests such as X ray, ECG and other tests performed during the management of adverse events.	[ ]
vi. I agree to take part in the above study and I know that this study is carried out only for the purpose of research.	[ ]
vii. I declare that I have not participated in any clinical study or donated blood within past 90 days	[ ]
viii. I hereby confirm that I will not participate in any other study or donate blood during the period of this study.	[ ]

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Authorization

I have read / been briefed on the above study and I voluntarily agree to participate in the project. I understand that participation in this study may not benefit me. Its general purpose, possible hazards, and inconveniences have been explained to my satisfaction. I hereby give my consent to participate in this study.

Name of the Subject	
Date of Birth	
Address of the Subject	
Occupation of the Subject:	Employed / Self-employed / Service / Housewife / others (Please tick appropriate)
Qualification of the Subject	
Annual Income of the Subject	
Name of the Nominee	
Relationship and Address of the Nominee	

I hereby declare that copy of duly filled Informed Consent Form was handed over to me.

Signature of subject	Date

Consent Obtained time: _____

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Investigator Declaration

I hereby declare that I have provided all the relevant information to the trial subject about the essential elements of clinical trial and the subject's rights to claim compensation in case of trial related injuries or death.

I also informed the subject or shall also inform his/her legal heirs of their rights to contact M/s Amaris Clinical, India and Ethics committee for the purpose of making claims in the case of trial related injury or death.

In case of trial related injury, I will request the Ethics committee to review and make recommendations for the payment for medical treatment as well as compensation for the trial related injury or death of the subject.

(Copies of the Patient Information Sheet and duly filled Informed Consent Form was handed over to the subject)

Name of the Investigator/Physician	**Signature**	**Date**

ANNEXURE II

PRESCRIBING INFORMATION OF TEGRETOL (CARBAMAZEPINE) 200MG NOVARTIS PHARMACEUTICALS CORPORATION EAST HANOVER, NEW JERSEY 07936.

NOVARTIS

Tegretol®

carbamazepine USP

Chewable Tablets of 100 mg - red-speckled, pink

Tablets of 200 mg – pink

Suspension of 100 mg/5 mL

Tegretol®-XR

(carbamazepine extended-release tablets)

100 mg, 200 mg, 400

mg Rx only

Prescribing Information

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO
OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10
TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL.
PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS** AND **PRECAUTIONS, LABORATORY TESTS**).

APLASTIC ANEMIA AND AGRANULOCYTOSIS

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH
THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER
THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS

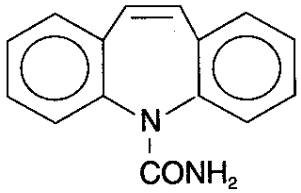
IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME.
HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.
BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA,
THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF
PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT
SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, XR tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5 mL (teaspoon). Its chemical name is 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients Tablets: Colloidal silicon dioxide, D&C Red No. 30 Aluminum Lake (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum. Tegretol-XR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200-mg tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Tegretol has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of Tegretol, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several in vivo animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of Tegretol has not been established.

Pharmacokinetics

In clinical studies, Tegretol suspension, conventional tablets, and XR tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the XR tablet slightly slower, than the conventional tablet. The bioavailability of the XR tablet was 89% compared to suspension. Following a b.i.d. dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Following a b.i.d. dosage regimen, Tegretol-XR tablets afford steady-state plasma levels comparable to conventional Tegretol tablets given q.i.d., when administered at the same total mg daily dose. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 µg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 µg/mL. In polytherapy, the concentration of Tegretol and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see PRECAUTIONS, Drug Interactions). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4-5 hours after administration of conventional Tegretol tablets, and 3-12 hours after administration of Tegretol-XR tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound Tegretol in serum. Because Tegretol induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, decreasing to 12-17 hours on repeated doses. Tegretol is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from Tegretol. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol.

The pharmacokinetic parameters of Tegretol disposition are similar in children and in adults. However, there is a poor correlation between plasma concentrations of carbamazepine and Tegretol dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an anticonvulsant in animal screens) in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10-15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

Epilepsy

Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia

Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated.

WARNINGS

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with Tegretol treatment. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Tegretol should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

SJS/TEN and HLA-B*1502 Allele

Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-B*1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity.

Across Asian populations, notable variation exists in the prevalence of HLA-B*1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but higher in some groups. HLA-B*1502 is present in <1% of the population in Japan and Korea.

HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans).

Prior to initiating Tegretol therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B*1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Tegretol should not be used in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN (see **WARNINGS** and **PRECAUTIONS, Laboratory Tests**).

Over 90% of Tegretol treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on Tegretol.

The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from Tegretol, such as anticonvulsant hypersensitivity syndrome or nonserious rash (maculopapular eruption [MPE]).

Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other antiepileptic drugs associated with SJS/TEN. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable.

Application of HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with Tegretol will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

Aplastic Anemia and Agranulocytosis

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Tegretol, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different

AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24%

among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebotreated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Tegretol or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

General

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

The use of Tegretol should be avoided in patients with a history of hepatic porphyria (e.g., acute intermittent porphyria, variegate porphyria, porphyria cutaneatarda). Acute attacks have been reported in such patients receiving Tegretol therapy. Carbamazepine administration has also been demonstrated to increase porphyrin precursors in rodents, a presumed mechanism for the induction of acute attacks of porphyria.

As with all antiepileptic drugs, Tegretol should be withdrawn gradually to minimize the potential of increased seizure frequency.

Usage in Pregnancy

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. There have also been reports that associate carbamazepine with developmental disorders and congenital anomalies (e.g., craniofacial defects, cardiovascular malformations, hypospadias and anomalies involving various body systems). Developmental delays based on neurobehavioral assessments have been reported. In treating or counseling women of childbearing potential, the prescribing physician will wish to weigh the benefits of therapy against the risks. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, if therapy is to be continued, monotherapy may be preferable for pregnant women.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m^2 basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect defects using currently accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal Tegretol and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have also been reported in association with maternal Tegretol use. These symptoms may represent a neonatal withdrawal syndrome.

To provide information regarding the effects of in utero exposure to Tegretol, physicians are advised to recommend that pregnant patients taking Tegretolenroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

PRECAUTIONS

General

Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac conduction disturbance, including second and third degree AV heart block; cardiac, hepatic, or renal damage; adverse hematologic or hypersensitivity reaction to other drugs, including reactions to other anticonvulsants; or interrupted courses of therapy with Tegretol.

AV heart block, including second and third degree block, have been reported following Tegretol treatment. This occurred generally, but not solely, in patients with underlying EKG abnormalities or risk factors for conduction disturbances.

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure have been reported (see ADVERSE REACTIONS and PRECAUTIONS, Laboratory Tests). In some cases, hepatic effects may progress despite discontinuation of the drug.

Multiorgan hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases (see ADVERSE REACTIONS, Other and PRECAUTIONS, Information for
Patients).

Discontinuation of carbamazepine should be considered if any evidence of hypersensitivity develops.

Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anticonvulsants including phenytoin and phenobarbital. A history of hypersensitivity reactions should be obtained for a patient and the immediate family members. If positive, caution should be used in prescribing carbamazepine.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, as well as dermatologic, hypersensitivity or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

Patients, their caregivers, and families should be counseled that AEDs, including Tegretol, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers

Tegretol may interact with some drugs. Therefore, patients should be advised to report to their doctors the use of any other prescription or nonprescription medications or herbal products.

Caution should be exercised if alcohol is taken in combination with Tegretol therapy, due to a possible additive sedative effect.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see WARNINGS, Usage in Pregnancy subsection). **Laboratory Tests**

For genetically at-risk patients (see WARNINGS), high-resolution '*HLA-B*1502 typing*' is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur (see PRECAUTIONS, General and ADVERSE REACTIONS). Carbamazepine should be discontinued, based on clinical judgment, if indicated by newly occurring or worsening clinical or laboratory evidence of liver dysfunction or hepatic damage, or in the case of active liver disease.

Baseline and periodic eye examinations, including slit-lamp, fundus copy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Interference with some pregnancy tests has been reported.

Drug Interactions

There has been a report of a patient who passed an orange rubbery precipitate in his stool the day after ingesting Tegretol suspension immediately followed by Thorazine®* solution. Subsequent testing has shown that mixing Tegretol suspension and chlorpromazine solution (both generic and brand name) as well as Tegretol suspension and liquid Mellaril® resulted in the occurrence of this precipitate. Because the extent to which this occurs with other liquid medications is not known, Tegretol suspension should not be administered simultaneously with other liquid medicinal agents or diluents (see DOSAGE AND ADMINISTRATION).

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to, the following:

Agents That May Affect Tegretol Plasma Levels

CYP 3A4 inhibitors inhibit Tegretol metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include:

> cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, fluvoxamine, nefazodone, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, azoles (e.g., ketaconazole, itraconazole, fluconazole), acetazolamide, verapamil, grapefruit juice, protease inhibitors, valproate.*

CYP 3A4 inducers can increase the rate of Tegretol metabolism. Drugs that have been shown, or that would be expected, to decrease plasma carbamazepine levels include: cisplatin, doxorubicin HCl, felbamate,[†]rifampin, phenobarbital, phenytoin, primidone, methsuximide, theophylline.

When carbamazepine is given with drugs that can increase or decrease carbamazepine levels, close monitoring of carbamazepine levels is indicated and dosage adjustment may be required.

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*increased levels of the active 10,11-epoxide

[†]decreased levels of carbamazepine and increased levels of the 10,11-epoxide

Effect of Tegretol on Plasma Levels of Concomitant Agents

Increased levels: clomipramine HCl, phenytoin, primidone

Tegretol induces hepatic CYP activity. Tegretol causes, or would be expected to cause, decreased levels of the following:

> acetaminophen, alprazolam, dihydropyridine calcium channel blockers (e.g., felodipine), cyclosporine, corticosteroids (e.g., prednisolone, dexamethasone), clonazepam, clozapine, dicumarol, doxycycline, ethosuximide,haloperidol, itraconazole, lamotrigine, levothyroxine, methadone, methsuximide, midazolam, olanzapine, oral and other hormonal contraceptives, oxcarbazepine, phensuximide, phenytoin, praziquantel, protease inhibitors, risperidone, theophylline, tiagabine, topiramate, tramadol, tricyclic antidepressants (e.g., imipramine, amitriptyline, nortriptyline), valproate, warfarin, ziprasidone, zonisamide.

In concomitant use with Tegretol, dosage adjustment of the above agents may be necessary.

Coadministration of carbamazepine with nefazodone results in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated (see CONTRAINDICATIONS).

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Concomitant use of Tegretol with hormonal contraceptive products (e.g., oral, and levonorgestrel subdermal implant contraceptives) may render the contraceptives less effective because the plasma concentrations of the hormones may be decreased. Breakthrough bleeding and unintended pregnancies have been reported. Alternative or back-up methods of contraception should be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Usage in Pregnancy

Pregnancy Category D (see WARNINGS).

Labor and Delivery

The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers

Tegretol and its epoxide metabolite are transferred to breast milk. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for Tegretol and about 0.5 for the epoxide. The estimated doses given to the newborn during breast-feeding are in the range of 2-5 mg daily for Tegretol and 1-2 mg daily for the epoxide.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Substantial evidence of Tegretol's effectiveness for use in the management of children with epilepsy (see INDICATIONS AND USAGE for specific seizure types) is derived from clinical investigations performed in adults and from studies in several in vitro systems which support the conclusion that (1) the pathogenetic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports a conclusion that the generally accepted therapeutic range of total carbamazepine in plasma (i.e., 4-12 mcg/mL) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No longer-term data from clinical trials is available.

Geriatric Use

No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system and skin (see BOXED WARNING), the liver, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) (see BOXED WARNING), pruritic and erythematous rashes, urticaria, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis; very rare cases of hepatic failure.

Pancreatic: Pancreatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.

Other: Multiorgan hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases. Signs or symptoms may include, but are not limited to fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly and abnormal liver function tests. These signs and symptoms may occur in various combinations and not necessarily concurrently. Signs and symptoms may initially be mild. Various organs, including but not limited to, liver, skin, immune system, lungs, kidneys, pancreas, myocardium, and colon may be affected (see PRECAUTIONS, General and PRECAUTIONS, Information for Patients).

Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, 3.2 g (a 24-year-old woman died of a cardiac arrest and a 24-year-old man died of pneumonia and hypoxic encephalopathy); children, 4 g (a 14-year-old girl died of a cardiac arrest), 1.6 g (a 3-year-old girl died of aspiration pneumonia).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within 1 week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe-ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (SEE TABLE BELOW)

Tegretol suspension in combination with liquid chlorpromazine or thioridazine results in precipitate formation, and, in the case of chlorpromazine, there has been a report of a patient passing an orange rubbery precipitate in the stool following coadministration of the two drugs (see PRECAUTIONS, Drug Interactions). Because the extent to which this occurs with other liquid medications is not known, Tegretol suspension should not be administered simultaneously with other liquid medications or diluents.

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A

low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Tegretol-XR is an extended-release formulation for twice-a-day administration. When converting patients from Tegretol conventional tablets to Tegretol-XR, the same total daily mg dose of Tegretol-XR should be administered. **Tegretol-XR tablets must be swallowed whole and never crushed or chewed.** Tegretol-XR tablets should be inspected for chips or cracks. Damaged tablets, or tablets without a release portal, should not be consumed. Tegretol-XR tablet coating is not absorbed and is excreted in the feces; these coatings may be noticeable in the stool.

Epilepsy (SEE INDICATIONS AND USAGE)

Adults and children over 12 years of age - Initial: Either 200 mg b.i.d. for tablets and XR tablets, or 1 teaspoon q.i.d. for suspension (400 mg/day). Increase at weekly intervals by adding up to 200 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age - Initial: Either 100 mg b.i.d. for tablets or XR tablets, or 1/2 teaspoon q.i.d. for suspension (200 mg/day). Increase at weekly intervals by adding up to 100 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Children under 6 years of age - Initial: 10-20 mg/kg/day b.i.d. or t.i.d. as tablets, or q.i.d. as suspension. Increase weekly to achieve optimal clinical response administered t.i.d. or q.i.d. ***Maintenance:*** Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions, and Pregnancy Category D).

Trigeminal Neuralgia (SEE INDICATIONS AND USAGE)

Initial: On the first day, either 100 mg b.i.d. for tablets or XR tablets, or 1/2 teaspoon q.i.d. for suspension, for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours for tablets or XR tablets, or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400-800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least

once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

Dosage Information

	Initial Dose			Subsequent Dose			Maximum Daily Dose		
Indication	Tablet*	XR†	Suspension	Tablet*	XR†	Suspension	Tablet*	XR†	Suspension
Epilepsy Under 6 yr	10-20 mg/kg/day b.i.d. or t.i.d.		10-20 mg/kg/day q.i.d.	Increase weekly to achieve optimal clinical response, t.i.d. or q.i.d.		Increase weekly to achieve optimal clinical response, t.i.d. or q.i.d.	35 mg/kg/24 hr (see Dosage and Administration section above)		35 mg/kg/24 hr (see Dosage and Administration section above)
6-12 yr	100 mg b.i.d. (200 mg/day)	100 mg b.i.d. (200 mg/day)	½ tsp q.i.d. (200 mg/day)	Add up to 100 mg/day at weekly intervals, t.i.d. or q.i.d.	Add 100 mg/day at weekly intervals, b.i.d.	Add up to 1 tsp (100 mg)/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hr		
Over 12 yr	200 mg b.i.d. (400 mg/day)	200 mg b.i.d. (400 mg/day)	1 tsp q.i.d. (400 mg/day)	Add up to 200 mg/day at weekly intervals, t.i.d. or q.i.d.	Add up to 200 mg/day at weekly intervals, b.i.d.	Add up to 2 tsp (200 mg)/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hr (12-15 yr) 1200 mg/24 hr (>15 yr) 1600 mg/24 hr (adults, in rare instances)		
Trigeminal Neuralgia	100 mg b.i.d. (200 mg/day)	100 mg b.i.d. (200 mg/day)	½ tsp q.i.d. (200 mg/day)	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 2 tsp (200 mg)/day in increments of 50 mg (½ tsp) q.i.d.	1200 mg/24 hr		

*Tablet = Chewable or conventional tablets † ®

XR = Tegretol -XR extended-release tablets

HOW SUPPLIED

Chewable Tablets 100 mg - round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100..... NDC 0078-0492-05

Unit Dose (blister pack)

Box of 100 (strips of 10)..... NDC 0078-0492-35

Do not store above 30°C (86°F). *Protect from light and moisture.*
Dispense in tight, light-resistant container (USP). Meets
USP Dissolution Test 1.

Tablets 200 mg - capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

Bottles of 100..... NDC 0078-0509-05

Do not store above 30°C (86°F). *Protect from moisture.*
Dispense in tight container (USP).
Meets USP Dissolution Test 2.

XR Tablets 100 mg - round, yellow, coated (imprinted T on one side and 100 mg on the other), release portal on one side

Bottles of 100..... NDC 0078-0510-05

XR Tablets 200 mg - round, pink, coated (imprinted T on one side and 200 mg on the other), release portal on one side

Bottles of 100..... NDC 0078-0511-05

XR Tablets 400 mg - round, brown, coated (imprinted T on one side and 400 mg on the other), release portal on one side

Bottles of 100..... NDC 0078-0512-05

Store at controlled room temperature 15°C-30°C (59°F-86°F). *Protect from moisture. Dispense in tight container (USP).*

Suspension 100 mg/5 mL (teaspoon) – yellow-orange, citrus-vanilla flavored

Bottles of 450 mL ..... NDC 0078-0508-83

Shake well before using.

Do not store above 30°C (86°F). *Dispense in tight, light-resistant container (USP).*

*Thorazine® is a registered trademark of GlaxoSmithKline.

NOVARTIS

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Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

REV: FEBRUARY 2009
T2008-29

ANNEXURE III

TEMPLATE FOR CASE

REPORT FORM

S#

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITION TERMS

AC	:	Amaris Clinical
AM	:	Ante Meridiem
BE	:	Bio-Equivalence
BMI	:	Body Mass Index
BP	:	Blood Pressure
CB	:	Cannula Block
CL	:	Clinical Research and Medical Affairs
CS	:	Clinically Significant
DBD	:	Difficulty in Blood Draw
ECG	:	Electrocardiogram
EQ	:	Equipment
F	:	Farenheit
IA	:	Intercurrent event
ICF	:	Informed Consent Form
ID	:	Identification
Kg	:	Kilogram
m^2	:	Square meter
Mg	:	milligram
Min	:	Minutes
mL	:	MilliLitre
mm Hg	:	Millimeters of Mercury
NCS	:	Not Clinically Significant
OTH	:	Others
P	:	Protocol
PM	:	Post Meridiem
PR	:	Pulse Rate
R	:	Reference
SOP	:	Standard Operating Procedure
SRL	:	Subject Reported Late
SVD	:	Sample Volume Deviation
SRE	:	Subject Reported Early
Temp.	:	Temperature
T	:	Test
Trt	:	Treatment

CHECK-IN RECORD

Volunteer Registration # AC ……

Date of Check-in: ……

INFORMED CONSENT

Volunteer Registration # AC…… **ICF Issuance (Date/Time): …….....**

ICF Obtained Time: ……... **Checked by: …….**

ALCOHOL BREATH TEST

Equipment ID: EQ/AC/CPG/AB/…….. **Time of Test: ……**

Test Result: ☐ Negative ☐ If Positive, Value …….mg/mL **Performed by: ……**

URINE DRUGS OF ABUSE

Sample ID: ……/19 **Sample Collection Time: …….. Collected by: ……...**

Test Result: ☐ Negative ☐ If Positive, specify …….

Time of Result: …… **Completed by: …….**

URINE PREGNANCY TEST ☐ **Not Applicable**

Sample ID: ……/19 **Sample Collection Time: …….. Collected by: ……...**

Test Result: ☐ Negative ☐ If Positive, specify …….

Time of Result: …… **Completed by: …….**

VITAL EXAMINATION AND SUBJECT WELL BEING

Method Used for Evaluation: Manual				**Posture:** Sitting		
BP (mm/Hg) (100 - 139/ 60 - 89 mmHg)	**PR (/min)** (60 - 100 /min)	**Oral Temp. (°F)** (97.0˚F-99.0˚F)	**Wellbeing**	**Time**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
			☐ Well ☐ Unwell			

Repeat Vitals Measurement ☐ **Not Applicable**

BP (mm/Hg) (100 - 139/ 60 - 89 mmHg)	**PR (/min)** (60 - 100 /min)	**Oral Temp. (°F)** (97.0˚F-99.0˚F)	**Wellbeing**	**Posture**	**Time**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
			☐ Well ☐ Unwell	☐ Sitting ☐ Supine			

CHECK-IN RECORD

INCLUSION AND EXCLUSION CRITERIA CHECK

Serial #	INCLUSION CRITERIA	
1.	Nonsmoking, Healthy males and/or non-pregnant, non-lactating female literate volunteers of 20 to 45 years (both years inclusive) with BMI of 18.5 – 24.9 Kg/m^2 for males and females.	□ YES □ NO □ Not Applicable
2.	Healthy volunteers as evaluated by medical history, vitals, (respiration rate between 12 and 20 breaths/minute) and general clinical examination.	□ YES □ NO □ Not Applicable
3.	Normal or clinically insignificant biochemical, hematological, urine and serology parameters.	□ YES □ NO □ Not Applicable
4.	Normal or clinically insignificant (ECG12-lead electrocardiogram) and Chest X ray.	□ YES □ NO □ Not Applicable
5.	Negative urine test for drugs of abuse, alcohol breath analysis for both males and females and negative pregnancy tests for females.	□ YES □ NO □ Not Applicable
6.	Subjects who are willing to practice acceptable methods of contraception.	□ YES □ NO □ Not Applicable
7.	Volunteers who can give written informed consent form and communicate effectively.	□ YES □ NO □ Not Applicable

Serial #	EXCLUSION CRITERIA	
1.	History of any major surgical procedure in the past 3 months.	□ YES □ NO □ Not Applicable
2.	History of any clinically significant cardiac, gastrointestinal, respiratory, hepatic, renal, endocrine, neurological, metabolic, psychiatric, hematological diseases.	□ YES □ NO □ Not Applicable
3.	Subject who consumed tobacco containing products within 48 hours prior to proposed time of dosing.	□ YES □ NO □ Not Applicable
4.	History of chronic alcoholism/chronic smoking/drug of abuse/ hypersensitivity.	□ YES □ NO □ Not Applicable
5.	Present or past history of intake of drugs or any prescription drug or over the counter (OTC) drugs within 14 days which potentially modify kinetics / dynamics of Atorvastatin Calcium or any other medication judged to be clinically significant by the investigator.	□ YES □ NO □ Not Applicable
6.	Consumption of grapefruit and/or its products within 10 days prior to the start of study.	□ YES □ NO □ Not Applicable
7.	Subject who had participated in any other clinical study or who had bled during the last 3 months.	□ YES □ NO □ Not Applicable
8.	Subjects who consume any xanthine containing food or drinks, citrus fruits and allied food (lime, lemon, orange and pomelo), alcoholic beverages and carbonated drinks such as cola during the stay in clinic and within 24 hours prior to dosing.	□ YES □ NO □ Not Applicable
9.	Positive test for HIV testing, Hepatitis B and C.	□ YES □ NO □ Not Applicable

Signature of the Physician / Investigator with Date	

CHECK-IN RECORD

SUBJECT MEDICAL EXAMINATION/ COMPLIANCE CHECK		
Serial #	**Description**	**Compliance**
1.	Any changes in health observed/informed by the subject	□ No □ if otherwise, specify……
2.	Checked the volunteer for prohibited substances	□ Yes □ if otherwise, specify……
3.	Does the subject comply with the restrictions as per protocol	□ Yes □ if otherwise, specify……
4.	Checked the ID card of the volunteer	□ Yes □ No
5.	Subject compliance verified for inclusion into the study from pages 03 and 05	□ Yes □ No

General Examination	□ No Abnormality Detected	□ If Abnormal specify,
Systemic Examination		
Cardio Vascular System	□ No Abnormality Detected	□ If Abnormal specify,
Respiratory System	□ No Abnormality Detected	□ If Abnormal specify,
Abdomen	□ No Abnormality Detected	□ If Abnormal specify,
Central Nervous System	□ No Abnormality Detected	□ If Abnormal specify,

Performed by (Physician/Investigator):

Subject Number Allotted	S…….

Check In Time:	**Check In Done by:**

ORAL DRUG DOSING RECORD

Drug Administration (Route of Administration: Oral)		
Date of Drug Administration		
Dosing procedure explained to subject	☐ Yes (✓ if yes, otherwise specify: …….)	
Subject Identity card verified	☐ Yes (✓ if yes, otherwise specify: ……)	
Treatment allotted for the subject		
☐ Test	☐ Reference	
Quantity	Scheduled Time	Actual Time
	08.30 AM	
Verifying Procedures		**Completed** (✓ If yes, otherwise specify)
Dosing Fluid (240 mL of water) consumed with drug		☐ **…….**
Subject's Mouth and hands checked		☐ **…….**
Treatment administered as per the label		
Drug Administered and Verified by:		
Supervised by:		

Comment(s): ☐ **Not Applicable**

Verified by (Investigator):

VITAL EXAMINATION AND STUDY SUBJECT WELLBEING RECORD

Method Used for Evaluation: ☐ Manual ☐ Automated (Multipara Monitor)	**Posture:** ☐ Sitting ☐ Supine

Time point (Hours)	**Scheduled Time**	**BP (mm/Hg)** (100 - 139/ 60 - 89 mmHg)	**PR (/min)** (60 - 100 /min)	**Wellbeing**	**Actual Time**	**Deviation (if any)**	**Recorded by**	**Investigator/ Physician comment(s) (if applicable)**
Date:								
00.00				☐ Well ☐ Unwell		☐ Yes ☐ No		
02.00				☐ Well ☐ Unwell		☐ Yes ☐ No		
08.00				☐ Well ☐ Unwell		☐ Yes ☐ No		

Time point (Hours)	**Scheduled Time**	**BP (mm/Hg)** (100 - 139/ 60 - 89 mmHg)	**PR (/min)** (60 - 100 /min)	**Oral Temp. (°F)** (97.0˚F - 99.0˚F)	**Wellbeing**	**Actual Time**	**Deviation (if any)**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
23.00					☐ Well ☐ Unwell		☐ Yes ☐ No		

Repeat Vitals Measurement							☐ **Not Applicable**	
Date	**BP (mm/Hg)** (100 - 139/ 60 - 89 mmHg)	**PR (/min)** (60 - 100 /min)	**Oral Temp. (°F)** (97.0˚F - 99.0˚F)	**Wellbeing**	**Posture**	**Time**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
				☐ Well ☐ Unwell	☐ Sitting ☐ Supine			
				☐ Well ☐ Unwell	☐ Sitting ☐ Supine			

VITAL EXAMINATION AND STUDY SUBJECT WELLBEING RECORD

Deviation(s) ☐ **Not Applicable**

Time Point	Reason for Deviation	Recorded by

Comment(s): ☐ **Not Applicable**

Verified by (Investigator/Physician):

HOUSING BLOOD SAMPLE COLLECTION RECORD

Volume of each blood sample(mL)	**05 mL**	**Type of Vacutainers**	**K_3EDTA**

Sample time point (Hours)	**Scheduled time of collection**	**Actual time of Collection**	**Deviation Codes**	**Collected By (Sign & Date)**
Day 01-Date:				
00.00				
00.50				
01.00				
01.50				
02.00				
02.50				
03.00				
03.33				
03.67				
04.00				
04.33				
04.67				
05.00				
05.33				
05.67				
06.00				
07.00				
08.00				
10.00				
12.00				
16.00				

Sample time point (Hours)	**Scheduled time of collection**	**Actual time of Collection**	**Deviation Codes**	**Collected By (Sign & Date)**
Day 02-Date:				

HOUSING BLOOD SAMPLE COLLECTION RECORD

Volume of each blood sample(mL)	**05 mL**	**Type of Vacutainers**	**K_3EDTA**

24.00				

Comment(s): ☐ **Not Applicable**

Verified by (Sign & date):

CHECK - OUT RECORD

Physical Examination	☐ No Abnormality Detected ☐ Abnormality Detected
Is the subject feeling well during check out	☐ Yes ☐ If otherwise, specify……
Is the subject withdrawn from the study	☐ No ☐ If otherwise, specify……
Is the subject being checked out prior to the completion of the housing period	☐ No ☐ If otherwise, specify……
Any ongoing adverse event during check out	☐ No ☐ If otherwise, specify……

Comment(s) ☐ **Not Applicable**

Verified by (Physician/Investigator)

Check Out Date/Time	**Check out Done by**

AMBULATORY RECORD

AMBULATORY (36 hours) Date: …….

Compliance Check

Serial #	Description	Compliance
1.	Any changes in health observed/informed by the subject	☐ No ☐ if otherwise, specify……
2.	Does the subject comply with the restriction as per protocol	☐ Yes ☐ if otherwise, specify……

Checked by:

Alcohol breath Test

Equipment ID: …….. Test result: ☐Negative ☐ If positive, Value …….mg/mL

Time of Test: …….. Performed by: ……..

Vital Examination and Subject Well being

Method Used for evaluation: Manual Posture: Sitting

Time point (Hours)	**Scheduled Time**	**Actual Time**	**BP (mm/Hg) 100-139/60-89mmHg)**	**PR (/min) (60-100/min)**	**Wellbeing**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
					☐ Well ☐ Unwell		

Repeat Vitals Measurement ☐ N/AP

Time point (Hours)	**Scheduled Time**	**Actual Time**	**BP (mm/Hg) 100-139/60-89mmHg)**	**PR (/min) (60-100/min)**	**Wellbeing**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
					☐ Well ☐ Unwell		
					☐ Well ☐ Unwell		

Sample Collection

Sample time point (Hours)	Scheduled time of collection	Actual time of Collection	Deviation Code	Collected by (Sign & date)
36.00				

AMBULATORY RECORD

AMBULATORY (48 hours) Date: …….

Compliance Check

Serial #	Description	Compliance
1.	Any changes in health observed/informed by the subject	☐ No ☐ if otherwise, specify……
2.	Does the subject comply with the restriction as per protocol	☐ Yes ☐ if otherwise, specify……

Checked by:

Alcohol breath Test

Equipment ID: …….. Test result: ☐Negative ☐ If positive, Value …….mg/mL

Time of Test: …….. Performed by: ……..

Vital Examination and Subject Well being

Method Used for evaluation: Manual Posture: Sitting

Time point (Hours)	**Scheduled Time**	**Actual Time**	**BP (mm/Hg) 100-139/60-89mmHg)**	**PR (/min) (60-100/min)**	**Wellbeing**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
					☐ Well ☐ Unwell		

Repeat Vitals Measurement ☐ N/AP

Time point (Hours)	**Scheduled Time**	**Actual Time**	**BP (mm/Hg) 100-139/60-89mmHg)**	**PR (/min) (60-100/min)**	**Wellbeing**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
					☐ Well ☐ Unwell		
					☐ Well ☐ Unwell		

Sample Collection

Sample time point (Hours)	Scheduled time of collection	Actual time of Collection	Deviation Code	Collected by (Sign & date)
48.00				

AMBULATORY RECORD

AMBULATORY (72 hours) Date: …….

Compliance Check

Serial #	Description	Compliance
1.	Any changes in health observed/informed by the subject	☐ No ☐ if otherwise, specify……
2.	Does the subject comply with the restriction as per protocol	☐ Yes ☐ if otherwise, specify……

Checked by:

Alcohol breath Test

Equipment ID: …….. Test result: ☐Negative ☐ If positive, Value …….mg/mL

Time of Test: …….. Performed by: ……..

Vital Examination and Subject Well being

Method Used for evaluation: Manual Posture: Sitting

Time point (Hours)	**Scheduled Time**	**Actual Time**	**BP (mm/Hg) 100-139/60-89mmHg)**	**PR (/min) (60-100/min)**	**Wellbeing**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
					☐ Well ☐ Unwell		

Repeat Vitals Measurement ☐ N/AP

Time point (Hours)	**Scheduled Time**	**Actual Time**	**BP (mm/Hg) 100-139/60-89mmHg)**	**PR (/min) (60-100/min)**	**Wellbeing**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
					☐ Well ☐ Unwell		
					☐ Well ☐ Unwell		

Sample Collection

Sample time point (Hours)	Scheduled time of collection	Actual time of Collection	Deviation Code	Collected by (Sign & date)
72.00				

ADVERSE EVENT RECORDING AND FOLLOW UP RECORD

☐ **NOT APPLICABLE**

SIGNS AND SYMPTOMS RECORD	
Pre-dose / Adverse Event Signs And Symptoms	**Recorded by (Sign & Date)**

Clinical Notes/Assessment	**Recorded by (Sign)**	**Date/Time**

ADVERSE EVENT RECORDING AND FOLLOW UP RECORD

☐ **NOT APPLICABLE**

Clinical Notes/Assessment	Recorded by (Sign)	Date/Time

ADVERSE EVENT RECORDING AND FOLLOW UP RECORD

☐ **NOT APPLICABLE**

Clinical Notes/Assessment	Recorded by (Sign)	Date/Time

Reviewed by:

Form # CL-145

ADVERSE EVENT RECORDING AND FOLLOW UP RECORD

CONCOMITANT MEDICATION

☐ **NOT APPLICABLE**

Date	Time	Indication	Medication Name (Generic & Brand Name)	Dose and Units	Frequency	Route of Administration	Administered by (Sign & Date)

Comment(s) ☐ **Not Applicable**

Completed by (Investigator/Physician)

Subject S# **CASE REPORT FORM** **Study: AC-P-XXX-YY**

Form # CL-145 SOP:

ADVERSE EVENT RECORDING AND FOLLOW UP RECORD Version: 01

ASSESSMENT OF ADVERSE EVENT ☐ **NOT APPLICABLE**

Adverse Event	Onset Date & Time	Period #/ Trt	Intensity	Action taken	Relationship to Study Drug	Outcome	Resolution Date & Time	Type of AE		Investigator/ Physician (Sign & Date)
								Expected/ Not	Serious/ Non	
			☐ Mild ☐ Moderate ☐ Severe	☐ Follow up ☐ Pharmacologic ☐ Non Drug Therapy ☐ Withdrawn	☐ Unrelated ☐ Possible ☐ Unlikely ☐ Probable	☐ Resolved ☐ Lost to follow up/ Unknown		☐ Expected ☐ Unexpected	☐ Serious ☐ Non-Serious	
			☐ Mild ☐ Moderate ☐ Severe	☐ Follow up ☐ Pharmacologic ☐ Non Drug Therapy ☐ Withdrawn	☐ Unrelated ☐ Possible ☐ Unlikely ☐ Probable	☐ Resolved ☐ Lost to follow up/ Unknown		☐ Expected ☐ Unexpected	☐ Serious ☐ Non-Serious	
			☐ Mild ☐ Moderate ☐ Severe	☐ Follow up ☐ Pharmacologic ☐ Non Drug Therapy ☐ Withdrawn	☐ Unrelated ☐ Possible ☐ Unlikely ☐ Probable	☐ Resolved ☐ Lost to follow up/ Unknown		☐ Expected ☐ Unexpected	☐ Serious ☐ Non-Serious	
			☐ Mild ☐ Moderate ☐ Severe	☐ Follow up ☐ Pharmacologic ☐ Non Drug Therapy ☐ Withdrawn	☐ Unrelated ☐ Possible ☐ Unlikely ☐ Probable	☐ Resolved ☐ Lost to follow up/ Unknown		☐ Expected ☐ Unexpected	☐ Serious ☐ Non-Serious	
			☐ Mild ☐ Moderate ☐ Severe	☐ Follow up ☐ Pharmacologic ☐ Non Drug Therapy ☐ Withdrawn	☐ Unrelated ☐ Possible ☐ Unlikely ☐ Probable	☐ Resolved ☐ Lost to follow up/ Unknown		☐ Expected ☐ Unexpected	☐ Serious ☐ Non-Serious	

Comment(s) ☐ **Not Applicable**

Verified by (Investigator/Physician)

POST STUDY EVALUATION RECORD

Date:

VITAL EXAMINATION AND SUBJECT WELLBEING							
BP (mm/Hg) (100 - 139/ 60 - 89 mmHg)	**PR (/min)** (60 - 100 /min)	**Oral Temp. (°F)** (97.0˚F-99.0˚F)	**Wellbeing**	**Posture**	**Actual Time**	**Recorded by**	**Physician/ Investigator comment(s) (if applicable)**
			☐ Well ☐ Unwell	☐ Sitting ☐ Supine			

SUBJECT MEDICAL EXAMINATION

☐ Performed at check out, (Refer check out record of Period II)

☐ No, (Record the examination details in the below table)

General Examination	☐ No Abnormality Detected	☐ Abnormality Detected,
Systemic Examination		
Cardio Vascular System	☐ No Abnormality Detected	☐ Abnormality Detected,
Abdomen	☐ No Abnormality Detected	☐ Abnormality Detected,
Respiratory System	☐ No Abnormality Detected	☐ Abnormality Detected,
Central Nervous System	☐ No Abnormality Detected	☐ Abnormality Detected,

Any ongoing adverse event ☐ No ☐ If Yes, refer adverse event recording form

Performed by:

☐ **Not Applicable**

ECG Examination

☐ Performed ☐ Not Performed Done by: **……**

☐ **Not Applicable**

Laboratory Evaluation

Sample ID: ……/19

Blood Sample: ☐ Collected ☐ Not Collected	**Time of Collection**	**……..…**	**Collected by**	**……..……**

POST STUDY EVALUATION RECORD

Date:

INTERPRETATION OF POST STUDY SAFETY ASSESSMENT			
Hematology	☐ Normal	If Abnormal, ☐ CS ☐ NCS	
Biochemistry	☐ Normal	If Abnormal, ☐ CS ☐ NCS	
Serum Pregnancy test	☐ Not Applicable	☐ Negative	☐ Positive
Interpreted by (Physician/Investigator)			

In case of Clinically Significant Abnormal value document the details in Form # CL-107 and follow up the subject

I have reviewed the vitals, ECG, lab parameters and performed general and systemic examination. I deem that the subject is

☐ **Recommended to Follow up**

☐ **Healthy**

Completed by (Physician/Investigator): .....

SUMMARY & CONCLUSION

6. SUMMARY & CONCLUSION

A major effective strategy for lowering the cost of medication, and thereby reducing its contribution to total healthcare costs, has been the introduction in global markets of generic equivalents of brand-name drugs (innovator drugs).

Assessment of "interchangeability" between the generic and the innovator product is carried out by a study of "*in vivo* equivalence" or "bioequivalence" (BE).

Now, many research has been done in recent years to develop new and more effective approaches to the assessment of BE. Thus, high-quality generic drugs at reduced costs have become available in every corner of the globe.

The BE study for new and generic products will be accepted through the approval of regulatory authorities. So, regulatory guidelines are necessary for conducting BE studies which have little differences as by country basis. Therefore, it is important to know the acceptance criteria for protocol design as per regulatory authority in BE study. Thus, comparison of regulatory requirements provides information for the safety and efficacy of the drug product.

CRO optimize their protocol designs with the goal of reducing complexity and cost, improving feasibility, and gathering more meaningful clinical data. The protocol design have impact on study budgets and on study execution feasibility. Thus, protocol plays a vital role in clinical study.

Carbamazepine is a narrow therapeutic drug which causes adverse effects due to small differences in the dose concentration. Thus, the protocol is important for the safety and efficacy of the drug Carbamazepine in the bioequivalence study.

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