



REVIEW: PHARMACOVIGILANCE -CLINICAL AND NON CLINICAL TRIALS OF RIVASTIGMINE.

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Abstract:

Pharmacovigilance promotes the safe and proper use of medications. Pharmacovigilance entails more than only assessing commercially available drugs and submitting this report to the national surveillance system. Pharmacovigilance efforts in India began far earlier than the launch of the country's official pharmacovigilance programme (PVPI) In India, several scientists, doctors, and administrators contributed to the field of pharmacovigilance. Pharmacovigilance's goal is to safeguard the public's health by discovering, assessing, and limiting safety concerns to make sure that the benefits of all medications outweigh the risks. The drug rivastigmine is the main subject of pharmacovigilance, which has expanded from being a small activity in drug control to a large one. The medication aids in the safety of clinical trials, the efficacy of adverse drug reactions, the development of safety for correct usage, and the right communication of that information to a variety of relevant stakeholder groups. Clinical research requires pharmacogenomics and Pharmacogenetics as essential components.

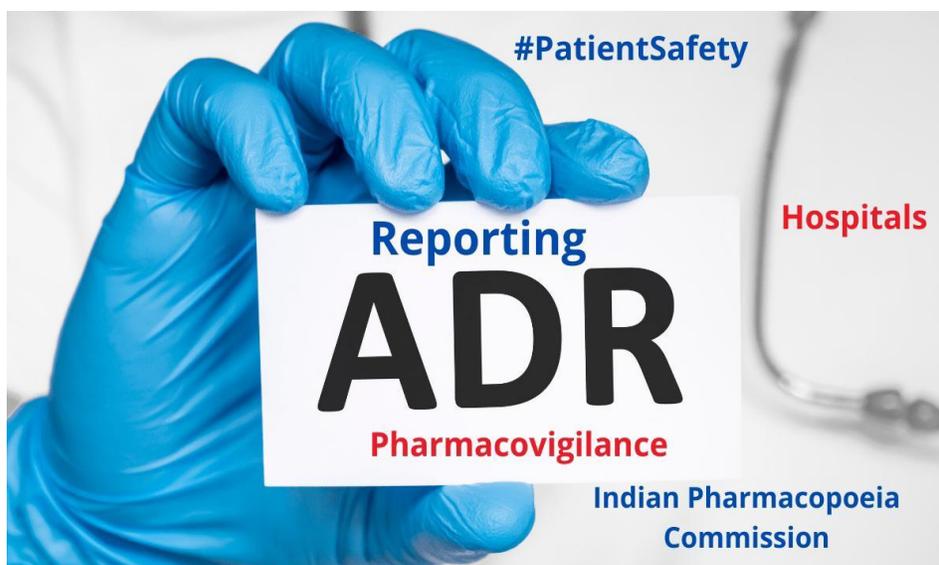
This pharmacovigilance review is outlined in the current pharmacovigilance review article as objectives drugs parts of the non clinical and clinical safety specification, efficacy selection of medicines marketing and post marketing service surveillance report, and adverse drug reaction report.

Key words:

pharmacovigilance, Objectives, Types, Component, Clinical Research ,ICH guideline, Clinical and Non clinical Safety, Selection and Selling of drugs, Identify adverse drug reaction, Consumption report, ADR Monitoring Form

Introduction:

Drug safety and pharmacovigilance are still active fields of clinical and scientific study. According to the World Health Organization, pharmacovigilance refers to scientific efforts connected to the detection, assessment, understanding, and prevention of adverse effects or any drug-related issues [1]. More than 65 countries have their own pharmacovigilance centers in 2002 according to . Adverse medication reactions are among the top 10 primary causes of death in various nations. In the pharmacovigilance programme for the next ten years, the prospective effects of such trends on assessments of science are briefly discussed. An significant unfavourable or unpleasant reaction caused by interventions connected to the use of a pharmaceutical product is what is known as an adverse drug reaction. The adverse drug reaction may be the define as the an appreciable harmful or the unpleasant reaction resulting from an the interventions related to the used of a medicinal product in which predicts to hazard from future administration and warrants prevention or specific treatment or the alternation of the dosage regiment or withdrawal of the product [2]. By encouraging the detection of unknown adverse drug reactions, identifying the risk factors for the development of adverse drug reactions, estimating quantitative aspects of the benefit and risk analysis, and disseminating information to improve drug prescribing and regulations, pharmacovigilance supports the safe and appropriate use of drugs. Pharmacovigilance goes beyond reviewing marketed drugs and includes more than just spontaneous reporting. India rises to become the third-largest country in the world for pharmaceutical output.

**❖ CONCEPT OF PHARMACOVIGILANCE:****▪ Pharmacovigilance:**

Pharmacovigilance also known as drug safety is the pharmaceutical science relating to the collection detection assessment monitoring and prevention of adverse drug effects with the pharmaceutical products.

- **Objectives Of Pharmacovigilance:**

- 1) The use of medications in conjunction with medical and paramedical interventions still needs to be improved in terms of patient care and safety.
- 2) The main goals of pharmacovigilance include demonstrating the efficacy of drugs by tracking their adverse effect profile over a long period of time from the lab to the pharmacy; monitoring any severe drug side effects; enhancing public health and safety in relation to the use of medications; encouraging the safe, logical, and economical use of medications; promoting understanding, education, and clinical training in pharmacovigilance; and effectively communicating to the public. [3]
- 3) Additionally, educating consumers, professionals, and regulators on the efficient use the goals of pharmacovigilance studies are achieved by creating programmers and methods for gathering and analysing information from patients and physicians as well as by designing research of the effects of medications. [3,4]
- 4) To improve patient care and safety.
- 5) To promote understanding and education of clinical training.
- 6) To achieve this goals National regulators and international organization should empower health care professionals and the public true report more adverse drug reaction.[5]

- **Types of Pharmacovigilance:**

There are four crucial techniques in pharmacovigilance, including

- 1) **passive monitoring**
- 2) **Active monitoring**
- 3) **Targeted Clinical Investigations**
- 4) **Cohort event monitoring**

- 1) **Passive monitoring:**

Utilizing spontaneous adverse event reports voluntarily reported to the marketing authorization holder or regulatory body is a component of passive surveillance approaches. Here, information on the negative effects is gathered and stored in a national or local database. Although the reporter's name is kept secret, the reporting forms can be used to retrieve patient-related information such as country, age, gender, and co-morbidities that already existed.

The following example of spontaneous reporting systems:

The FDA maintains the FAERS (FDA Adverse Event Reporting System) database.[6]

- 2) **Active Monitoring:**

This approach intends to track particular adverse drug events and determine the total number of adverse drug reactions using a pre-planned procedure. It is often referred to as safety monitoring or toxicity monitoring.[7]

3) Cohort Event Monitoring:

In this approach, the surveillance study is prepared before the medication treatment even starts. A group of individuals is exposed to a drug for a predetermined amount of time and is closely monitored throughout treatment. Monitoring is done for adverse drug interactions or those connected to one or more medications taken along with the target drug.[8]

4) Targeted Event Monitoring

These types of studies are carried out to identify and define the negative effects of a medicine among certain populations, such as those with certain genetic abnormalities, pregnant women, and senior citizens.[9]

- **Component of Pharmacovigilance:**

- 1) Adverse event Case Management including expedited reporting
- 2) Aggregate Reporting
- 3) Signal Intelligence
- 4) Risk management

- 5) **Adverse Event Case Management including expedited reporting:**

Even in absence of an the adverse event, medications errors such as an overdosing, drug addiction, misuse, and exposure to drugs . while the pregnant or nursing are importance to since they may be the result in a negative pharmacological reactions. [10] The data required for pharmacovigilance are provided through information obtained from patients and healthcare professionals via pharmacovigilance agreements, as well as from other sources including the medical literature. Most nations require the license holder (often a pharmaceutical corporation) to provide adverse event data to the local drug regulatory authority in order to market or test a pharmaceutical product. (See Adverse event reporting below.)

2) Aggregate Reporting:

Reports that place more of an emphasis on overview, evaluation of the safety profile, and benefit-risk analysis are referred to as aggregate reports.

- Periodic Safety Update Reports /Periodic Benefit Risk Evaluation Reports
- Periodic Adverse (Drug) Experience Reports
- Development Safety Update Reports
- Integrated Summaries of Safety
- Clinical Summaries of Safety (EU)[11]

1) Periodic Safety Update Reports (PSURs) / Periodic Benefit Risk Evaluation Reports (PBRERs),:

Periodic Safety Update Reports (PSURs), PSUR Submission Requirements, PSUR Single Assessment Procedures (PSUSAs), and the European Union Reference Dates (EURD) list are all covered on this page. In order to assess the risk-benefit ratio of a medical product at specific intervals following its authorization, pharmacovigilance records called PSURs are used. The purpose of the PSUR is to give a thorough and critical examination of the product's risk-benefit ratio, taking into consideration fresh or previously unrecognized safety data in the context of accumulated risk and benefit knowledge.[12]

2) Periodic Adverse Drug Experience Report:

Periodic Adverse Drug Experience Reports (PADER/PAER) are required to be provided to the US Food and Drug Administration as part of post-cumulative safety reports (USFDA). A PADER's major objective is to update, assess, and offer information on a medicine's global data as well as medication safety. Along with the assessment of the drug's benefit-risk profile, it offers a concise overview of any updated post-approval information. This assessment offers information about whether more labelling changes for medications or further research are necessary.[13]

3) Development safety update reports:

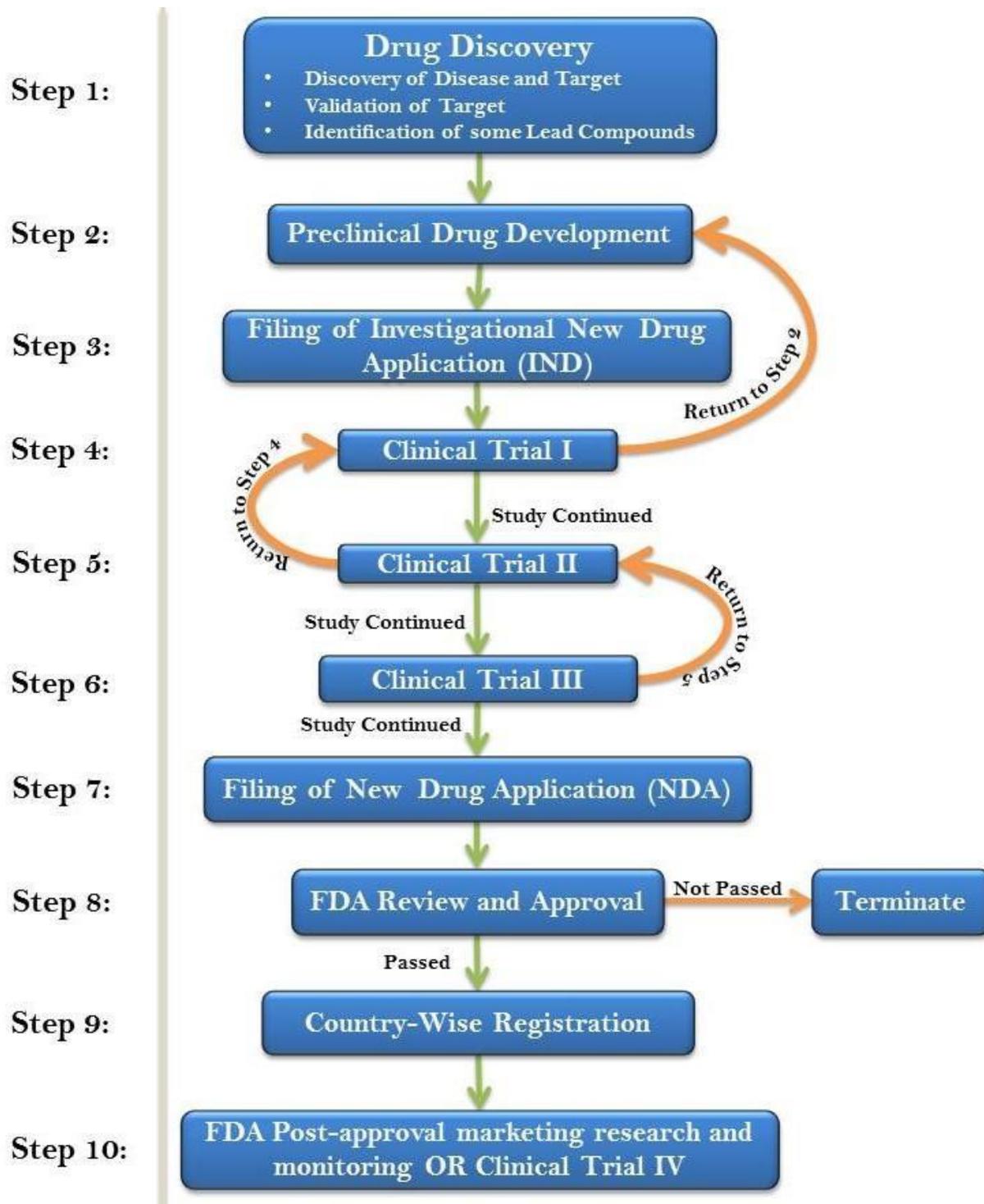
DSURs are new, globally standardised safety documents that cover the safety summary of pharmaceuticals while they are in the development or clinical trial phases. They became required in European Union member states in September 2011. The PSUR format, which is already used for updating the safety record of medications in their marketing phase, served as the foundation for the new DSUR, as stated in ICH guideline E2F. The former European Union ASR (Annual Safety Report) and US IND Annual Report formats have been replaced by the new DSUR format.[14]

4) Integrated summarize of safety: The NDA's integrated summary of safety (ISS) section presents thorough safety data gathered during the development period.[15]

3) Signal intelligence:

Pharmacovigilance signal intelligence are practice focused on adopting DPA algorithms to the mine SRS(Spontaneous Reporting System) data for constituting hypotheses of the signal drug of AE combinations that needed for the investigations to the establish evidence is based on medicine to confirm its associations between the those pairs. Then they regulatory actions may be taken to the protected to the public health.

❖ CLINICAL RESEARCH :



❖ Definition: Clinical Trials -

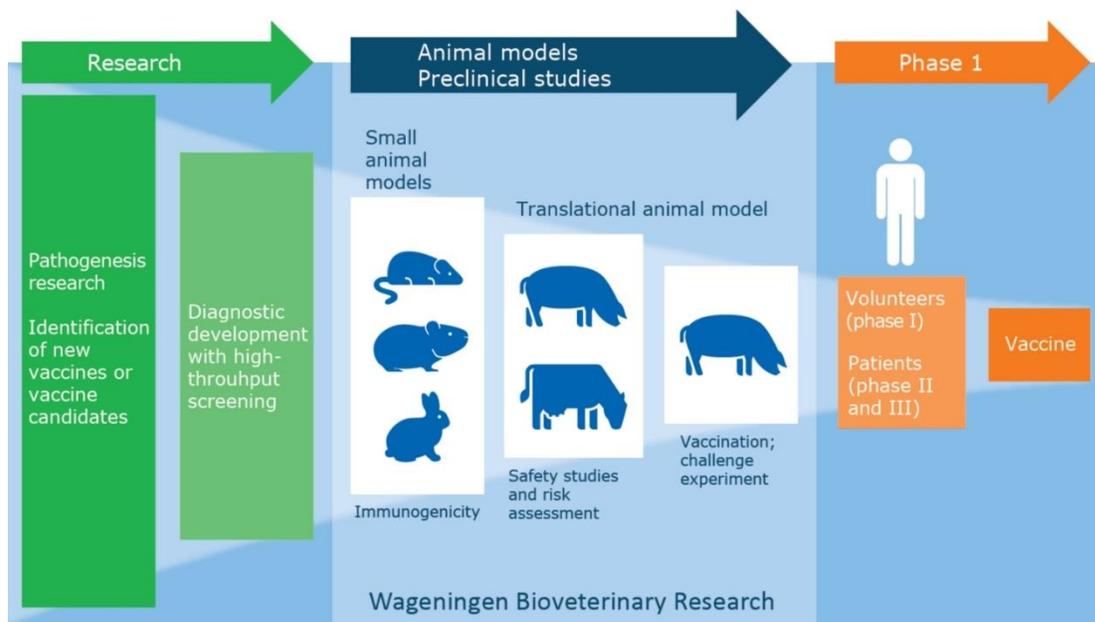
Clinical trials is a prospective ethically designed investigation in human subjects to objectively discover verify /compare the results of two or more therapeutic measures.

❖ **Classification:**

- 1) Pre-clinical Trials:
- 2) Clinical Trials:

1) **Pre-clinical Trials:**

- Research using animals to find out if a drug, procedure, or treatment is likely to be useful. Preclinical studies take place before any testing in humans is done. In drug development, preclinical development, is termed as the preclinical studies or nonclinical studies, is stage of research that begins to before the clinical trials (testing in humans) and during which is important to the feasibility, inter reactive testing and drug safety data are collected, typically in laboratory animals in clinical trials studies.[16]

❖ **Following types of steps are performed:**1) **Screening Test:**

The screening test is done by the detect potential health disorders or diseases in the people who do not have any symptoms of these disease. The goals is early to detection and the lifestyle changes or to surveillance, reduce the risk disease, or to detect the early enough to treat the most effectively. This test simple and rapidly preformed test to indicate present or absent of a perticular Pharmacodynamics activity that is sought for. Ex- Analgesic or hypoglycemic activity.

2) **Test on isolated organs, bacterial culture:**

These are also preliminary test to detect specific activity such as anti histaminic vasodilator antibacterial etc. When evaluating potential contamination, the clinician should assess the patient's clinical presentation and determine whether he or she shows signs and symptoms of bacteremia.

3)Taste on animal model of human diseases:

Such as kindled scissors in rats spontaneously hypersensitive rights experimental tuberculosis in mouse along than induced diabetes in rats or dogs.

[16]

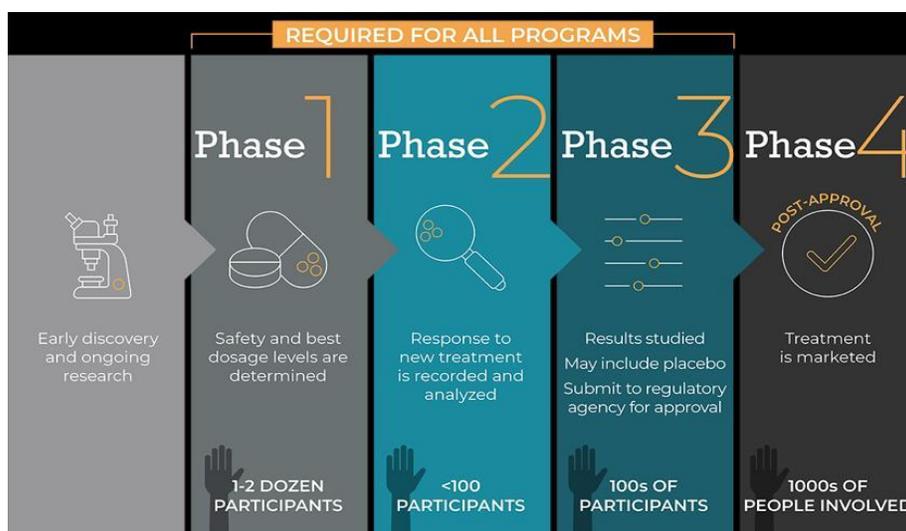
Four types of animal models are used in preclinical research:

- (1) disease induction models
- (2) xenograft animal mode

❖ Clinical Trials:

When a compound deserving trial in man is identified by animal, studies, the regulatory authorities are approached who an satisfaction tissue an Investigational new drug (IND) licence. Standerd for design, ethics, conduct, monitoring, auditing, recording and anything data , reporting and clinical trials in the form of good clinical practice guidelines by an International conference on Harmonization on ICH. National agency in most countries including ICMR (Indian council of Medical Research) in India, it is also form by ethical guideline for ethical trials.

The clinical studies are divided into 4 phases.



1) Phase-0(Microdosing Study):

This is a new strategy being developed to reduce the cost and time of the drug development process. One such tool is a microdosing human study undertaken before phase first trial and is also called as a phase 0 study. The Microdosing study undertaken before phase 1 trials, is also call as phase 0 study. A very low dose about 1/100 of the estimated human dose and maximum 100 Microdosing. The phase 0 are studied that the Microdosing pharmacokinetics may be different form that at pharmacology dose.

2) Phase:1(Human pharmacology and safety)

The first human administration of the drug is carried out by clinical pharmacologist and tried physician in the sitting where vital functions and emergency and recitative facilities are available .Lowest estimated dose(1/100-1/10 of the highest dose producing no toxicity in animal) The important emphasis is on safety tolaribility and functions heart rate bronchipasam kidney and liver damage. The side Effects are noted and Pharmacodynamics effects are known in man. The human Pharmacokinetics parameters of the drug are measured for the first time.

3) Phase:3-Therapeutic exploration and dose ranging:

This is conducted by physicians who trend as clinical in investigation and involves 100 to 50 500 patient selected by inclusion and exclusion criteria in therapeutic exploration and dose ranging. **A study that tests the safety and how well a new treatment works compared with a standard treatment.** For example, phase III clinical trials is compare to which group of the patients has been better to survival the rates or fewer side effects. Restricted marketing permission for use only in hospitals with specific monitoring facilities or only by specially trained physicians may be granted in case of toxic drugs they are found useful in the serious or otherwise incurable diseases.

4) phase 4-postmarketing surveillance/ data gathering studies:

After the drug has been marketed for general use ,practicing physicians are identify through whom data are collected on a structured perform about the efficacy, acceptability and adverse effect of the drug in the real field situation (similar to prescription or event monitoring.)

Patients treated in the normal course from the study populations numbers therefore much larger. Uncommon adverse effect or those that occur only after long term use and unsuspected drug interaction are detected in this stage. further therapeutic trials involve special groups like children', elderly , pregnant/ lactating, women patient with renal /hepatic diseases. Modified release dosage forms additional roots of administration fixed dose drug combinations may be explored. Most drugs continue their development even after marketing.[16]

- **Functions:**

- 1)**Drug controller General of India (DCGI):**

The Central Drugs Standard Control Organization is led by the Drug Controller General of India (DCGI) (CDSCO).

- 1) The primary drug authority in India is called CDSCO.
- 2) The Ministry of Health and Family Welfare is home to the national-level regulatory organization known as CDSCO.
- 3) The organization is in charge of approving licences for specific drug categories. Its main office is in New Delhi.
- 4) Under CDSCO, there are six operational central drug testing laboratories.
- 5) The DCGI also sets requirements for the production, marketing, import, and distribution of medicines in India.
- 6) Medical and pharmaceutical equipment are likewise governed by the DCGI.
- 7) The DCGI is the appellate authority in cases of disagreement over the drug's quality.
- 8) The national reference standard for drugs is created and updated by the DCGI.[17]

2) Central drug standard control organization (CDSCO):

- 1) The Drugs and Cosmetics Act's drug approval process.
- 2) clinical studies establishing guidelines for medications.
- 3) Drug imports are subject to quality control.
- 4) coordinating the efforts of state drug enforcement agencies.
- 5) Registration of foreign producers of pharmaceuticals and medical equipment whose goods will be imported.
- 6) granting of permits by government hospitals or medical institutions to import medications for their patients' usage.
- 7) Encourage the prohibition of medications deemed dangerous or inadequately therapeutic under Section 26A of the Drugs and Cosmetics Act.[17]

3) Investigational New Drug (IND)

To be transported or supplied over state borders, a medicine must first be the subject of an approved marketing application, according to current Federal law. A sponsor must apply for an exception from that legal requirement because it is likely that it will want to transport the experimental medicine to clinical investigators in numerous states. [18]

- Studies on the pharmacology and toxicology of animals: provide preclinical information that can be used to determine if a substance is reasonably safe for use in human trials.
- Information on the manufacturing process: Including the manufacturer, stability, and controls used to create the drug material and the drug product.
- Clinical Protocols and Investigator Information – Extensive protocols for suggested clinical research to determine whether preliminary trials may subject participants to unneeded hazards. [18]

4) New drug application:

The New Drug Application has served as the foundation for the regulation and control of new pharmaceuticals in the United States (NDA). Since 1938, an authorised NDA has been required for every new medicine before it may be sold in the United States. Medicine sponsors can officially request that the FDA approve a novel drug for sale and marketing in the United States through the NDA application. The information obtained for an Investigational New Drug (IND) during animal studies and human clinical trials is included in the NDA.[19]

5) Abbreviated new drug application:

When submitted to the FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, an Abbreviated New Drug Application (ANDA) comprises information that allows for the examination and eventual approval of a generic drug product. Since preclinical (animal) and clinical (human) evidence to show safety and efficacy are typically not necessary, generic drug applications are known as "abbreviated" applications. A generic applicant must instead prove through science that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). To offer the American public a secure, cost-effective alternative, an applicant may produce and commercialize the generic drug product after receiving approval.[20]

❖ ICH Guidelines:

▪ Objectives of ICH Guidelines:

- 1) To give a brief outline of the development of Good Clinical Practice (International Conference on Harmonisation)
- 2) To highlight the significance of adhering to ICH GCPs when conducting clinical trials.
- 3) To comprehend the obligations of the parties involved, including the committees, sponsors, and researchers.
- 4) To talk about crucial GCP topics like patient recruitment, consent, and data privacy.
- 5) To understand the effects of non-compliance.[21]

▪ Scope:

- 1) All laboratories that perform tests on biological samples for patient care, disease control, and research should follow good clinical laboratory practises, such as:
 - I), microbiology and serology
 - ii) Blood banking and haematology
 - III) Molecular Pathology and Biology
 - Iv) Clinical Patholog
 - V) Clinical Biochemistry
 - Vi) Histopathology/Pathology and Cytology
 - Vii) Immunology (Immunohematology and Immuno biochemistry); [22]

▪ New drug and clinical trial rule 2019-

The government of India announced the New drugs and clinical trials regulations 2019 (New rules) on March 19.

o Modifications affecting clinical study registration and biological and health research.

The significant adjustments to the ethics committee (EC) following the implementation of the new Drug and Clinical Trials Regulations are summarised in this paper.

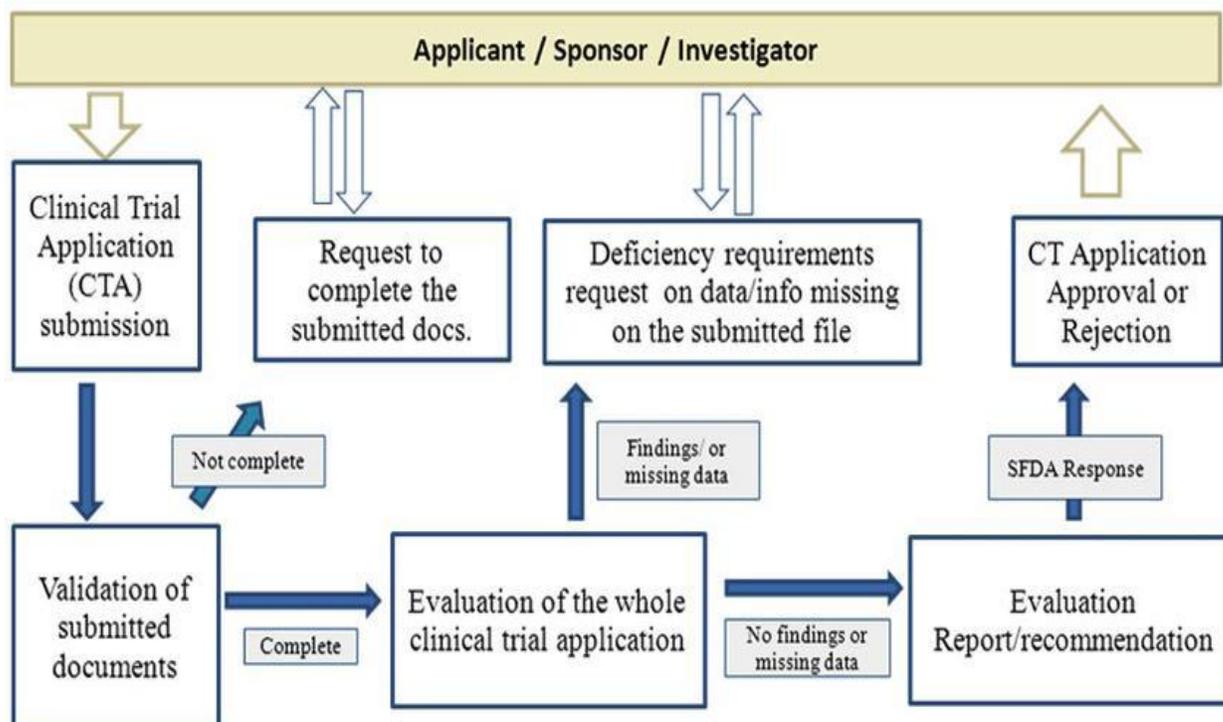
This document the summarizes major changes affecting ethics committee (EC) after the coming into force of the new Drug and Clinical Trials Rules 2019.

The EC is the required to follow the requirements set as per new rules and to forward their report to central licensing authority.[23]

- **Clinical trial protocol design:**

Every clinical research starts with the creation of the clinical protocol. The protocol is a document that outlines the objective design methodology, statistical considerations, and organizational structure of a clinical trial. It also ensures the safety of trial participants and the accuracy of the data collected. The study's title page (general information)

- Objectives/purpose
 - Study design
 - Selection and exclusion of subject
 - Treatment of subjects
 - Assessment of Efficacy
 - Assessment of safety
 - Adverse Events
 - Discontinuation of the study
 - Statistics
 - Quality control and Assurance
 - Ethics
 - Data handling and Record keeping[24]
- **Process of clinical trials Application:**



❖ ELEMENTS OF THE NON-CLINICAL AND CLINICAL SAFETY SPECIFICATIONS:**▪ Objective**

- 1) This recommendation is meant to help with planning pharmacovigilance actions, particularly in advance of a new drug's early postmarketing period (in this recommendation, the phrase "Drug" refers to chemical substances, items generated from biotechnology, and vaccines).
- 2) The Safety Specifications and the Pharmacovigilance Plan are presented with a licence applications are the primary topics of this guideline
- 3) For regions that favour this strategy, the guideline can be used by sponsors to create a stand-alone document.
- 4) It can also be used to provide instructions on the how to incorporate elements of the Safety Specifications and the Pharmacovigilance Plan into the Common Technical Document (CTD).
- 5) The recommendation outlines a process for summarizing significant known risks associated with a drug, significant potential risks, and significant gaps in knowledge, such as populations that may be at risk. [25]

▪ Scope:

The goal of this recommendation is to offer a structure for a Pharmacovigilance Plan and a Safety Specification that lists the known and foreseeable risks associated with the product that will be covered by the Plan. The following sections make up the guideline:

Pharmacovigilance Plan

Safety Specification

Annex – Pharmacovigilance Methods.

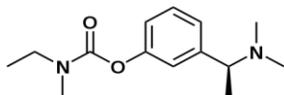
It is advised that business pharmacovigilance specialists participate early in product development. Any significant new benefit or risk information should be reviewed and used to amend the Plan when the various Plan components are put into action.

This recommendation is supported by the following guidelines:

- Effective coordination between regulators and industry;
- Planning of pharmacovigilance activities across the product life cycle;
- Science-based approach to risk documentation
- Applicability of the Pharmacovigilance Plan throughout the three ICH areas[25]

❖ **Pre-clinical:**

- Drug-Rivastigmine
- Molecular formula: C₁₄H₂₂N₂O₂
- Structure:



- Molecular weight –250.34
- Dates:

Modified.	Create
2022/10/31.	2005/08/08
- Brand Names: Exelon
- Revastigmine (exelon) is approved for mild to moderate Alzheimer's diseases .It is taken as pill. A Skin patch is available that serve Alzheimer diseases. Revastigmine is a colinergic inhibitors used for the treatment of mild to moderate Alzheimer's diseases. The drug can be administrated orally or via a transdermal patch.

▪ **History:**

Marta Weinstock-Rosin of the Hebrew University of Jerusalem's Department of Pharmacology created rivastigmine, which Yissum then sold to Novartis for further commercialization. It is a physostigmine semi-synthetic derivative. [26]

▪ **Pharmacokinetics:**

Rivastigmine is well absorbed with a absolute bioavailability is about to 40% (3-mg dose). It is linear pharmacokinetics up to the 3 mg BID but is non-linear at the higher doses. The dose from 3 to 6 mg BID results in the 3-fold increase in AUC. The elimination half-life is about to 1.5 hours, is most elimination as the metabolites via through the urine.

Absorption: Rivastigmine is the rapidly and completely absorbed. Peak plasma concentrations is reached in the approximately to 1 hour. Absolute bioavailability after a 3-mg dose is about 36%. Administration's of Exelon with the food delays to the absorption (t_{max}) by 90 minutes, lowers C_{max} by approximately 30% and the increases AUC by approximately 30%.

Distribution: It is a approximately distributed throughout the body with a volume of distributions in the range of 1.8-2.7 L/kg. Rivastigmine penetrates the blood brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. Rivastigmine is about 40% bound to the plasma proteins at the concentrations of 1-400 ng/mL, which cover the therapeutic concentration range. The rivastigmine distributes to equally between the blood and plasma with a blood-to-plasma partition ratio of the 0.9 at concentrations ranging from 1-400 ng/mL

Metabolism: Rivastigmine is rapidly and extensively metabolized, primarily cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Based on evidence from in vitro animal studies, the major cytochrome P450 isozymes are minimally involved in rivastigmine metabolism.

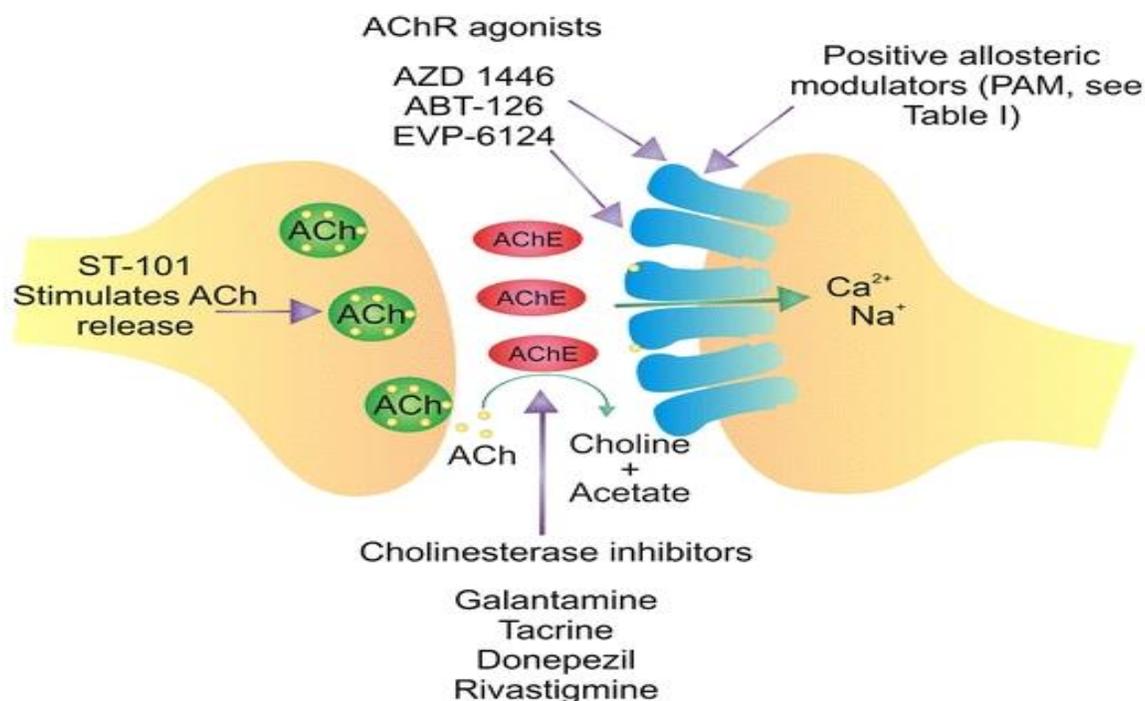
Elimination: The major pathway of elimination is via the kidneys. Following administration of ¹⁴C-rivastigmine to 6 healthy volunteers, total recovery of radioactivity over 120 hours was 97% in urine and 0.4% in feces. No parent drug was detected in urine. The sulfate conjugate of the decarbamylated metabolite is the major component excreted in urine and represents 40% of the dose. Mean oral clearance of rivastigmine is 1.8 ± 0.6 .

- **Pharmacodynamics**

Rivastigmine is a parasympathomimetic and a reversible cholinesterase inhibitor. An early pathophysiological feature of Alzheimer's disease that is associated with memory loss and cognitive deficits is a deficiency of acetylcholine as a result of selective loss of cholinergic neurons in the cerebral cortex, nucleus basalis, and hippocampus. Tacrine is postulated to exert its therapeutic effect by enhancing cholinergic function. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, rivastigmine's effect may lessen as the disease progresses and fewer cholinergic neurons remain functionally intact[28].

- **Mechanism of action**

Rivastigmine is a carbamate derivative that is structurally related to physostigmine, but not to donepezil and tacrine. The precise mechanism of rivastigmine has not been fully determined, but it is suggested that rivastigmine binds reversibly with and inactivates cholinesterase (e.g. acetylcholinesterase, butyrylcholinesterase), preventing the hydrolysis of acetylcholine, and thus leading to an increased concentration of acetylcholine at cholinergic synapses. The anticholinesterase activity of rivastigmine is relatively specific for brain acetylcholinesterase and butyrylcholinesterase compared with those in peripheral tissues.[29]



- Food Interactions

The drug with food Administered rivastigmine capsules with the food delays absorption but increases the AUC[30]

- **Drug Drug Interaction:**

Acebutolol may make Rivastigmine's bradycardia effects worse.

Acetylcholine When Rivastigmine and Acetylcholine are combined, there is a possibility that the risk or severity of side effects will rise. [31]

Toxicity:

A carbamate cholinesterase inhibitor called rivastigmine is used to treat dementia. With symptoms of both muscarinic (salivation, lacrimation, urine, faeces, miosis, bronchorrhea, and bradycardia) and nicotinic (muscle weakness, fasciculations, and paralysis) stimulation, the toxicity is anticipated to resemble poisoning from other carbamates and organophosphates. We present a case of transdermal patch-induced rivastigmine toxicity. After the patches were removed, the patient's symptoms and signs spontaneously improved without the need for atropine or oxime therapy. The symptoms of enhanced nicotinic, muscarinic, and central nervous system effects should be recognised by emergency physicians (seizure)[32]

Efficacy:

The efficacy is a centrally active cholinesterase inhibitor, rivastigmine in patients with the advanced moderate Alzheimer's disease (AD) is evaluated in a 12-month placebo-controlled research, the effectiveness of rivastigmine tartrate (ENA713), a centrally active cholinesterase inhibitor, was assessed in individuals with advanced moderate Alzheimer's disease (AD). Our goal was to find out if there was any proof that rivastigmine was helpful for patients with advanced illness. These patients and matching

controls were compared. In this trial, rivastigmine was administered for 12 months to 24 patients with advanced moderate AD. Twenty other patients received a placebo. At 3, 6, 9, and 12 months, the higher-dose group's average daily dosages of rivastigmine were 6.1 1.0, 8.3 1.2, 8.9 1.3, and 10.7 1.6 mg/day, respectively.[33,34]

▪ **Adverse Drug Reactions:**

Vomiting
Nausea
Stomach pain
Diarrhoea
Loss of appetite

❖ **Clinical Trials:**

1) Safety Monitoring During Clinical Trials:

Rivastigmine was approved for clinical use based on the largest pre approval database for all statins prior to commercial use. In this database rivastigmine had a similar safety profile to the highest approval dose is 40 mg.

2) Discovery And Developments:

Novel medications were being developed to combat the harmful effects of neurodegenerative disorders at the turn of the 20th century as awareness of these conditions grew. Rivastigmine was one of the major medications that was developed in 1985. Rivastigmine was approved by the FDA in 1997 for the treatment of mild to moderate Alzheimer's disease. Additionally, it can be used to treat mild to moderate dementia linked to Parkinson's disease.[35]

Clinical Research:

Phase-1

- Patient inclusion criteria:
 - Ages over- 50 to 90
 - Male/ female
 - 12 month long clinical trials.
 - Adult patients 50 to 90 years of age.
 - Probable Alzheimer diseases based on the National institute neurologically and communication disorders and strock.
 - Body mass index between 18 and 36 kg /m2 at screening.
 - Patient with Cornell scale for depression in dementia (CSDD)scores.
 - Receiving treatment of with donepezil or Rivastigmine for at least 6 month before baseline. Revastigmine through patient on tablet prior to 3 months are eligible they must on the patch formulation only in stable dose 4.6 mg/ 24 hours or 9.5 mg/ 24 hours patch for 3 months before.[36]

- **Patient Exclusion Criteria:**

- Any neurological or psychiatric condition not specified in expectation in protocol.
- Background of mental retardation.
- UnControlled behaviour symptoms.
- Alcohol/ substances abuse or depndance.
- Unstable are clinically significant cardiovascular diseases expected to progress require or changes during study period and the assessment of the clinical or mental status of the patient.
- Inadequate hepatic ,renal or thyroid function.
- Positive for hepatitis B, hepatitis C, or HIV infection.
- Poorly controlled diabetes.
- Requiring nursing home care pysotropic medication as defined by protocol.[36]

Phase -2:

Phase IIa, multi-center, double-blind, placebo-controlled study of a new buccal film of montelukast in patients with mild to moderate Alzheimer’s Disease. Study drug is administered once or twice daily for 26 weeks, and treatment effect is assessed to primarily using the global NTB composite scores at the Week 26.

Patients is consent to participate will be the undergo screening assessments to the determine eligibilities. This study is to enroll the patients who are ≥ 50 years of age with the mild to moderate Alzheimer’s Disease and on a stable treatment to donepezil, rivastigmine or galantamine for the ≥ 3 months. Patients is randomized to one of two treatment groups

Group A: Montelukast buccal film

Group B: Matching placebo buccal film

Details

Condition.	Alzheimer Disease
Treatment.	Montelukast buccal film, Placebo buccal film
Clinical Study Identifier	NCT03402503
Sponsor.	ntelGenx Corp.
Last Modified on.	28 October 2022[36]

Phase -3

In phase 3 double blind trials we randomly assigned 1012 and 1040 patient respectively with mild to moderate. Alzheimer’s diseases to receive placebo or solanezumab every 4 week for 18 month. The primary outcome were the changes from baseline to week 80 in the 11 item cognitive subscale of the Alzheimer’s diseases assessment scale.[36]

Phase-4

phase IV study evaluating safety, tolerability and effectiveness of rivastigmine 27 mg -15 cm² transdermal patch to prescribed in the patients with to severe dementia of the Alzheimer's type as per the discretion of treating physician.

Details

Condition	Alzheimer's Disease
Treatment	Rivastigmine
Clinical Study Identifier	NCT02989402
Sponsor	Novartis Pharmaceuticals
Last Modified on.	11 October 2022[36]

❖ **Post-marketing Monitoring**

The post-marketing surveillance (PMS) study was to described of safety/tolerability of treatments with the rivastigmine capsules in the patients with Alzheimer's diseases. The post-marketing is observational study in the patients who is the criteria for the mild or moderate Alzheimer's disease. The primary outcomes measure for this trial is the incidence of emerging adverse events. Dosages related to the titration patterns and to maintenance the doses were summarized. This secondary objectives of the study is to define the optimal titrations pattern, to maintenance dose, efficacy and patient satisfaction with the treatment of rivastigmine capsules.

❖ **SELECTION AND SELLING OF DRUGS:**▪ **Commercial availability of Rivastigmine Drug:**

India-based Manus Akteva Biopharma LLP is an ISO 9001:2015 Certified Global Supplier for the drug Rivastigmine, also known by its chemical name 123441-03-2. Based on the product's accessibility through our network, we provide Rivastigmine, 123441-03-2 from our manufacturer, supplier, or principals for your research and development, evaluation, or commercial needs. We can also provide intermediates of Rivastigmine, 123441-03-2 along with the supporting technical set needed for evaluation. We also make it simple for manufacturers, suppliers, and principals to access low-cost, premium raw materials.

Product information documents contain:

- summary of the product characteristics (annex I);
- The manufacturing authorisation holder is responsible for the batch release (annex IIA);
- This conditions of the marketing authorisations (annex IIB);
- An labelling (annex IIIA);
- The package leaflet (annex IIIB)[37]

▪ **Selling Of Drug:**

Revastigmine exports shipments from India are 3.5k exported by 87 suppliers. Top 3 products categories of rivastigmine in exports from India are:

- 1) HSN code 30049099:HS:pituitary hormones; prednisolone; danazole and other progesterone and oestrogen group hormone other.
- 2) HSN code 29242990:HS:Other
- 3) HSN code 29420090:HS:diloxanide famotidine other.

India export most hits revastigmine to United State ,United Kingdom and Germany. The top first exporter of revastigmine are India. India is the largest exporter of Rivastigmine and account for 3475 shipment.

India Export Data:

Data available form	December 2012
Data update till August	2022
Update Frequency	Monthly
Data Average	T3(30%40)
Number of shipment	316455748
India export data shipment	270 4750
Country covered	240
Numbers of suppliers	612933
Data Availability mode	Online /offline

India Import Data:

Date	14 November 2016
Indian port	Bombay cargo
CTH	293090 99
Item Description	Revastigmine are isomer are isomer USP rs (20 mgx 5 vials) (impurities standard for r & d stability)
Quantity	5
VQC	Nos
V.P.VSD-	4.89
Asses USD	24.47
COO	United States
Duty	India import

- **Consumer information of Rivastigmine:**
- **About this medication:**

Rivastigmine is one group of drug known as cholinesterase inhibitor which is used for the treatment of the symptoms of patient with mild to moderate Alzheimer's diseases or with dementia occurring at least 2 years following the diagnosis of Parkinson's diseases.
- **Symptoms :**
 - Progressive memory loss
 - Increasing confusion
 - Behaviour changes
 - Difficult to carry out activities of daily living.
- **Medications:**

This medication should only be taken after proper diagnosis of your condition has been made by your doctor.
- **What is What it does:**

People with Alzheimer's disease have decreased levels of acetylcholine, a substance which is found in the brain and which is thought to be necessary for memory and other mental functions. EXELON® works by inhibiting the enzyme (acetylcholinesterase) which breaks down the acetylcholine. This in turn increases the amount of acetylcholine in the brain. EXELON® is the treatment on the symptoms, not a cure of the disease. In the clinical studies with the EXELON®, most of the patients with an Alzheimer's disease improved the memory and other mental functions, or showed no further decline, as compared to placebo (sugar tablet) for up to 6 months. However, EXELON® may take as long as 12 weeks to begin working, and patient response to this medicine will vary.
- **Medical Ingredients:**

EXELON® contains the active substance rivastigmine hydrogen tartrate.
- **Dosage form comes in:**
 - **Capsule:** Each hard gelatin capsule contains 1.5, 3.0, 4.5 or 6.0 mg of rivastigmine as rivastigmine hydrogen tartrate.
 - **Oral Solution:** Each mL of oral solution contains 2 mg of rivastigmine as rivastigmine hydrogen tartrate.
- **Usual Dose:**

Your doctor will tell you what dosage of EXELON® to take, starting with a low dose and gradually increasing, depending on how you respond to the treatment. The highest dose that should be taken is 6 mg twice a day (12 mg/day). To benefit from your medicine you must take it every day. If you have questions about how long to take of the EXELON®, talk to your doctor or your pharmacist.

- **Overdose:**
Some people who have accidentally taken too much oral EXELON® have experienced nausea (feeling sick), vomiting (being sick), and diarrhea. You may become dehydrated (losing too much fluid) if vomiting or diarrhea are prolonged. Some people may also experience high blood pressure, hallucinations, slow heart beat and fainting
- **Side Effects:**
Feeling sick (nausea), being sick (vomiting), diarrhea, stomach Discomfort after meal, stomach pains and loss of appetite; dizziness, headache, sleepiness, drowsiness, agitation, confusion, nightmares, anxiety; weakness, fatigue, a general feeling of being unwell;
- **How to store it:**
 - ☑ Do not use EXELON® after the expiry date.
 - ☑ Store EXELON® at room temperature (15 - 30°C). Do not refrigerate or freeze in the EXELON® of oral solution.
 - ☑ Store EXELON® Oral Solution in the original package in an upright position.
 - ☑ Keep EXELON® in a safe place and out of the reach and sight.[38]

❖ **Pharma companies of web portals:**

- 1) Exelon -Novartis(India Ltd.) Capsule
- 2) Capsule Exelon (3 mg) - Novartis India Ltd.
- 3) Exelon capsule (4.5 mg) – Novartis India Ltd
- 4) Rivamer capsule – Torrent pharmaceutical. Ltd
- 5) Rivamer capsule – sun pharmaceuticals Industries Ltd.
- 6) Rivasmine Capsule – Cipla Ltd
- 7) Srivasmine Capsule – Cipla Ltd
- 8) Zeemine tablet (1.5 mg)- psyco Remedies.[39]

❖ **identification of adverse drug reaction of a selected drug using different search engines (eg- Medscap.com,drugs.com)**

9) Greater than 10%:

- Nausea (20-25%)
- Diarrhoea (11-15%)
- Vommiting (11-15%)

10) 1-10%:

- Abdominal pain
- Anorexia
- Muscle camp
- Fatigue
- Dizziness
- Headache
- Weight loss
- Depression

- Isomnia
- UTI
- Anaemia
- Breadcardiya[40]

❖ Adverse Drug Reaction Monitoring Form:



Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION (National Coordination Centre-Pharmacovigilance Programme of India) Ministry of Health & Family Welfare, Government of India Sector-23, Raj Nagar, Ghaziabad-201002								FOR AMC/NCC USE ONLY			
Report Type <input type="checkbox"/> Initial <input type="checkbox"/> Follow up								AMC Report No. _____			
A. PATIENT INFORMATION								Worldwide Unique No. _____			
1. Patient Initials _____		2. Age at time of Event or Date of Birth _____		3. M <input type="checkbox"/> F <input type="checkbox"/> Other <input type="checkbox"/>		4. Weight _____ Kgs		12. Relevant tests/ laboratory data with dates			
B. SUSPECTED ADVERSE REACTION								13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)			
5. Date of reaction started (dd/mm/yyyy)								14. Seriousness of the reaction: No <input type="checkbox"/> if Yes <input type="checkbox"/> (please tick anyone) <input type="checkbox"/> Death (dd/mm/yyyy) <input type="checkbox"/> Congenital-anomaly <input type="checkbox"/> Life threatening <input type="checkbox"/> Required intervention to Prevent permanent impairment/damage <input type="checkbox"/> Hospitalization/Prolonged <input type="checkbox"/> Disability <input type="checkbox"/> Other (specify) _____ 15. Outcomes <input type="checkbox"/> Recovered <input type="checkbox"/> Recovering <input type="checkbox"/> Not recovered <input type="checkbox"/> Fatal <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Unknown			
6. Date of recovery (dd/mm/yyyy)											
7. Describe reaction or problem											
C. SUSPECTED MEDICATION(S)											
S.No	8. Name (Brand/Generic)	Manufacturer (If known)	Batch No. / Lot No.	Exp. Date (If known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates		Indication	Causality Assessment
								Date started	Date stopped		
i											
ii											
iii											
iv											
S.No as per C	9. Action Taken (please tick)						10. Reaction reappeared after reintroduction (please tick)				
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unkn own	Yes	No	Effect unknown	Dose (if reintroduced)	
i											
ii											
iii											
iv											
11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)											
S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates		Indication				
					Date started	Date stopped					
i											
ii											
iii											
Additional Information:								D. REPORTER DETAILS			
								16. Name and Professional Address: _____			
								Pin: _____ E-mail: _____			
								Tel. No. (with STD code) _____			
								Occupation: _____ Signature: _____			
								17. Date of this report (dd/mm/yyyy): _____			
Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.											

❖ **Adverse Drug Reaction Monitoring Form:**

- 1) WHO Policy Perspectives on Medicines. Geneva: WHO; 2004. Geneva: World Health Organization. Looking at the Pharmacovigilance: ensuring the safe use of medicines. Available from:
 - 2) http://www.whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf [cited on 2009 Dec 15] [Google Scholar] [Ref list]
 - 3) Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356: 1255–59.2.
 - 4) WHO, Pharmacovigilance: ensuring the safe use of medicines, Geneva: WHO 2004.
 - 5) Livio F, Renard D, Buclin T. Pharmacovigilance Rev Med Suisse 2012;8:116-5)
 - 6) <https://images.app.goo.gl/qHxxypeeqTasJTV7>
 - 7) Methods in Pharmacovigilance - (https://isoonline.org/wp-content/uploads/2015/09/21052015_Methods-in-PhV.pdf)
 - 8) SKS Methods in Pharmacovigilance - (<https://www.glocaluniversity.edu.in/files/eContent/eBpharm/SKS%20Methods%20in%20Pharmacovigilance.pdf>)
 - 9) Adverse drug reactions vs side effects - <http://www.myhealth.gov.my/en/adverse-drug-reactions-vs-side-effects/>)
 - 10) Adverse Drug Events, Adverse Drug Reactions and Medication Errors - (<https://www.pbm.va.gov/PBM/vacenterformedicationsafety/tools/AdverseDrugReaction.pdf>)
 - 11) **International Drug Monitoring: The Role of National Centers"** (PDF). Who-umc.org. Retrieved February 27, 2015..
 - 12) <https://www.scratch-pv.com/main-indications/aggregate-reports/?lang=en#:~:text=Aggregate%20Reports%20refers%20to%20those,They%20comprise%20e.g.&text=or%20safety%20related%20parts%20of%20Clinical%20Study%20Reports.>
 - 13) Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report - Explanatory note (PDF/301.89KB) First published: 06/04/2017
Last updated: 29/04/2020
EMA/670256/2017 Rev.3
 - 14) [https://www.freyrsolutions.com/what-is-a-pader#:~:text=Periodic%20Adverse%20Drug%20Experience%20Report%20\(PADER%20FPAER\)%20is%20a,provide%20information%20about%20drug%20safety.](https://www.freyrsolutions.com/what-is-a-pader#:~:text=Periodic%20Adverse%20Drug%20Experience%20Report%20(PADER%20FPAER)%20is%20a,provide%20information%20about%20drug%20safety.)
 - 15) <https://trilogywriting.com/development-safety-update-report/https://www.rhoworld.com/3-key-questions-when-developing-the-integrated-summary-of-safety-issue>
 - 16) [Essential Medicinal Pharmacology by kD Tripathi , Edition 8th 2018.](#)
 - 17) <https://byjus.com/free-ias-prep/drug-controller-general-of-india-dcgi/>
 - 18) Investigational New Drug (IND) <https://www.fda.gov/investigational-new-drug-ind-application>
 - 19) New Drug Application (NDA) <https://www.fda.gov/new-drug-application-nda>
 - 20) Abbreviated New Drug Application (**ANDA**)

<https://www.fda.gov/abbreviated-new-drug-application-anda-generics>

- 21) <https://slideplayer.com/amp/9485721/>
- 22) <https://www.slideshare.net/anubhavsingh184007/presentation-on-good-clinical-practices-gcp-by-anubhav-singh-mpharm-1st-year>
- 23) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7034142/>
- 24) <https://hub.ucsf.edu/protocol-development>
- 25) 25) CIOMS, Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V. Geneva; World Health Organization (WHO), 2001.
- 26). Guidelines for Good Pharmacoepidemiology Practices (GPP), International Society for Pharmacoepidemiology, http://www.pharmacoepi.org/resources/guidelines_08027.cfm, August 2004.
- 27) https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020823s016,021025s008lbl.pdf
- 28) Cholinergic drugs in pharmacotherapy of Alzheimer's disease. Mini Rev Med Chem. 2002 Feb;2(1):11-25. [Article]
- 29) Rosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stahelin HB, Hartman R, Gharabawi M: Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ. 1999 Mar 6;318(7184):633-8. [Article]
- 30) Finkel SI: Effects of rivastigmine on behavioral and psychological symptoms of dementia in Alzheimer's disease. Clin Ther. 2004 Jul;26(7):980-90. [Article]
- 31) Rosler M, Retz W, Retz-Junginger P, Dennler HJ: Effects of two-year treatment with the cholinesterase inhibitor rivastigmine on behavioural symptoms in Alzheimer's disease. Behav Neurol. 1998;11(4):211-216.
- 32) Doody R.S. Stevens J.C. Beck C. Dubinsky R.M. Kaye J.A. Gwyther L. et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001; 56: 1154-1166
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- 34) Gauthier S: Clinical Diagnosis and Management of Alzheimer's Disease. London, Martin Duniz Ltd, 1999, pp 57-67, 249-269.
- 35) Henderson EJ, Lord SR, Brodie MA, Gaunt DM, Lawrence AD, Close JC, Whone AL, Ben-Shlomo Y. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPOND): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol. 2016 Mar;15(3):249-58. [PubMed]
- 36) <https://www.centerwatch.com/clinical-trials/listings/136837/a-phase-ii-multicenter-randomized-double-blind-parallel-group-placebo-controlled-study-to-investigate-the-efficacy-and-safety-of-ro4602522-added-to-the-background-therapy-of-the-acetylcholinesterase-inhibitors-donepezil-or-rivastigmine-in-patients-with-2/?q=rivastigmine&query=rivastigmine&featured=true&rnk=1>
- 37) <https://www.ema.europa.eu/en/medicines/human/EPAR/rivastigmine-actavis>

- 38) https://www.ask.novartispharma.ca/download.htm?res=exelon_patient_e.pdf&resTitleId=118
- 39) <https://www.medindia.net/drug-price/rivastigmine.htm>
- 40) <https://reference.medscape.com/drug/razadyne-er-galantamine-343059#4>