Study of the Quinine drug related to Pharmacovigilance

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CLINICALRESEARCH

❖ **Defineandphasesofclinicaltrials:**

➢ **Definition:**

Clinical trials are prospective biomedical or behavioural research studies on humanparticipants designed to answer specific questions about biomedical or behaviouralinterventions, including new treatments and known interventions that warrant furtherstudyand comparison.

➢ **Preclinicaltrials**

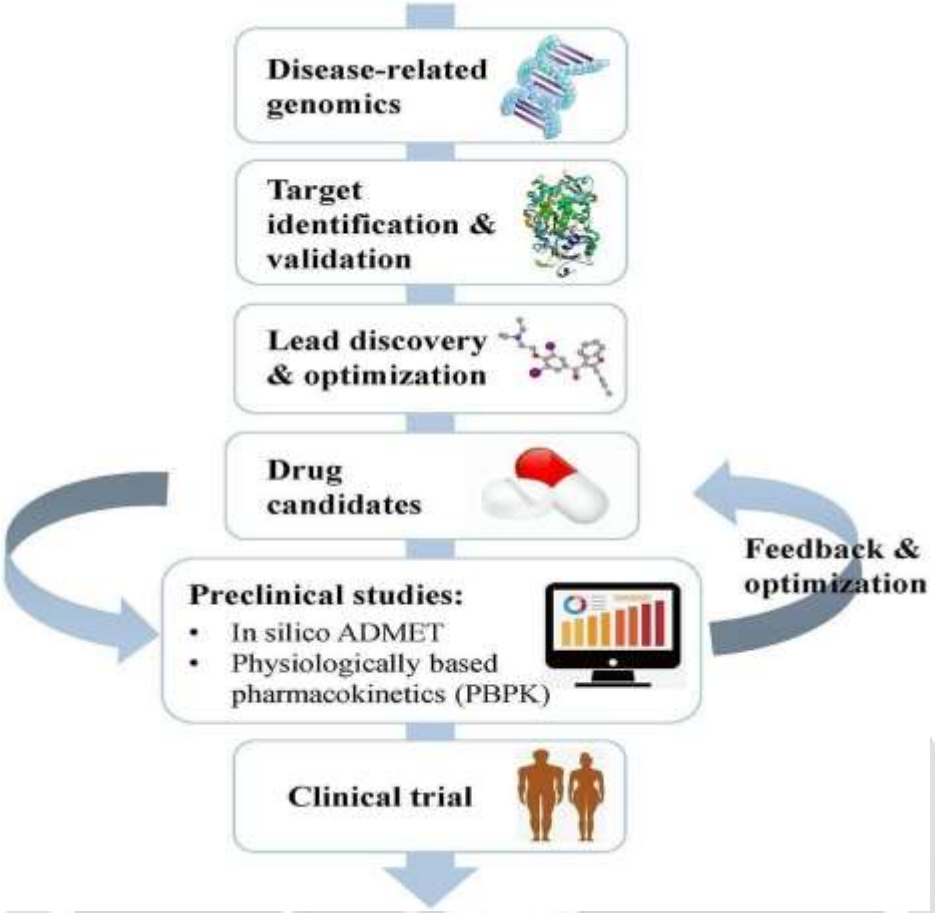
Introduction

Details of non-clinical/per-clinical studies are discussed under ICH m3 guidance.The Non-clinical study recommendations for the marketing approval of apharmaceutical product include:

safety pharmacology studies repeated dose toxicityStudies toxicokinetics and non-clinical pharmacokinetic studies reproduction toxicitystudiesandgenotoxicitystudies.

ATypicallybothInvitroandInVivotestswillbeperformedStudiesofdrug

toxicity includes which organs are targeted by that drug, as well if there are any longterm Carcinogeniceffectsortoxiceffects causing illne



Phasesofpreclinicaltrials

1. **Safetypharmacology:-**
   The core safety Pharmacology study includes the assessment of affectcardiovascular, central nervous, respiratory the consideration is given to an any invivo valuation as addition to general toxicity. Care should be taken to reduce numberofanimalused

2. **Toxicokinetic&Pharmacokineticstudies:-**
   In vitro metabolic data for animals and humans & expose data in animals to priorinitiating human clinical trials. Further absorption, distribution, metabolism andexcretioninanimalsshould beavailablefortreadinglongduration.

3. **Acutetoxicitystudies:-**
   This information has been obtained From single dose toxicity studies in twomammation species using both the clinical and parenteral route of administration.This available to phase III clinical trials for higher risks overdose eg. Depression,pain, dementia.

4. **RespectedDosetoxicity:**
   In principle the duration of animal toxicity studies conducted in two mammalsspecies.

5. **Local Tolerancestudies:-**
   To evaluate local tolerance by the intended therapeutic bouts as a part of the generaltoxicity studied. To support limited human adm by non-therapeutic rough eg. (singleIV).
6. **Genotoxicitystudies:-**

An assay for gene mutation is generally considered sufficient to support all singledoseclinicaldevelopment trials.

7. **Carcinogenicitystudies:-**

   Itshouldbeconductedforthemarketingapplication.

   For pharmaceutical development treat certain serious diseases for adults paediatricspatientscarcinogenicitytesting.

8. **Reproductivetoxicity:-**

   It is Should be conducted as appropriate as the population that is to be exposed.There are four categories: women not of child bearing, women of child bearing inpregnantwomen.

9. **Othertoxicity:-**

   Non-clinicalstudyeg.identifypotentialbiomarkers

➢ **Clinicaltrials**

- **Introduction**

The clinical trials are the Research studies performed in the people that are aimed atevaluatingmedical,surgicalorbehaviouralinterventionthatiscalledclinicaltrials.

Theevolutionofthemodernclinicaltrialdatesbackatleastto theeighteenthcentury. Lind, in his classical study on board the Salisbury, evaluated six treatmentsfor scurvy in 12 patients. One of the two who was given oranges and lemonsrecovered quickly and was fit for duty after 6 days. The second was the bestrecovered of the others and was assigned the role of nurse to the remaining tenpatients. Several other comparative studies were also conducted in the eighteenthand nineteenth centuries. The comparison groups comprised literature controls, otherhistoricalcontrols,andconcurrentcontrols.

- **Phasesofclinicaltrials**

1. **Phase 0:-**

   The Phase-0 trials are the exploratory trials that also exist as small clinical trials thatinvolvedosingatasub-therapeutic level.

   Therapy area-any indicationDosage-subtherapeuticdosing

   Trial length -usually Less than one weekItinvolves 10 to15patients

2. **Phase 1:-**

Phase 1 trials are the first studies of an investigational new drug in humans.Phase 1 trials may be conducted in individuals who have the disease the drug isintendedtotreat.
The Phase-1 has a duration of 1 month to 12 months.Phase1generallyinvolvesbetween 20to30patients.

3. **Phase 2:-**

phase 2 clinical trials tense detector more about how safe the treatment is and nowwillitworkDoctoralsotestwhetheranewtreatmentworksforaspecificcancer.
It is approximately 33% of drugs.Theduration is12to24months.
Itinvolvednomorethanseveral 100patients.

4. **Phase 3:-**

The main objective of phase 3 is to verify the therapeutic action of a new substanceinalargenumberofpatientstodeterminetherisk /benefitreaction.
Theduration is1to4 years.
Ithas300to3000volunteersinvolved.

5. **Phase 4:-**

A type of clinical trials that studies the side effects caused over time by a newtreatment after it has been approved and is a market this trious 100k side effects thatwere not seen in earlier trials that may study how well a new treatment works over alongperiod.
Itsdurationisaminimumoftwo years.
Itinvolves severalthousandvolunteerswhohavethedisease.

❖ **FunctionofDrugControllerGeneralofIndia(DCGI)**

➢ DCGI lays down the standard and quality of manufacturing, selling, import anddistributionofdrugsinIndia.
- Preparationandmaintenanceofnationalreferencestandards.
- TobringaboutuniformityintheenforcementoftheDrugsandCosmeticsAct.
- Training of Drug Analysts deputed by State Drug Control Laboratories and otherInstitutions.
- Analysis of Cosmetics received as survey samples from CDSCO (central drugstandardcontrolorganisation)

➢ Withthenotificationof MedicalDeviceRules2017bytheGovernmentofIndia,DCGI will also act as Central Licensing Authority (CLA) for the medical devices which fallunder the purview of these rules. Out of four Classes of medical devices from ClassA to Class D, DCGI will be the direct licensing authority for Class C and Class Ddevices, whereas it will coordinate licensing for Class A and B devices through Statedrugcontrollers,who willact asStateLicensingAuthorityorSLA.

❖ **FunctionofCentralDrugStandardControlOrganization(CDSCO)**

➢ Under the Drug and Cosmetics Act, the regulation of manufacture, sale anddistribution of Drugs is primarily the concern of the State authorities while the CentralAuthorities are responsible for approval of New Drugs, Clinical Trials in the country,laying down the standards for Drugs, control over the quality of imported Drugs,coordination of the activities of State Drug Control Organisations and providingexpert advice with a view of bring about the uniformity in the enforcement of theDrugsandCosmeticsAct.

❖ **Typesofregulatoryapplication:**

➢ **InvestigationalNewDrug(IND)**

A drug that has not been approved for general use by the food and drugadministration but is under investigation in clinical trials regarding its safety andeffectiveness first by clinical investigators and then by practising physicians usingpatients who havegiveninformedconsentto participate.

- **Duration**

30 days an IND application may 90 into effect 30 days after FDA receives theapplication unless FDA notifies the sponsor that the investigations described in theapplication are subjected to a clinical hold or on career notification by FDA that theclinicalinvestigations inthe INDmaybegin.

➢ **NewDrugApplication(NDA)**

The identify and contact information of the sponsor and the phase of the trials. Acommitment that an IRB will be responsible for initial and continuing review of Thetrials. The name of the drug is a list of its active ingredient and its dosage and routeof Administration. The objective and planned duration of the proposed clinical trials.Identitiesandqualifications ofall investigators

- **Duration**

Submission of an NDA is the form step asking the FDA to consider a drug formarketing approval. The FDA has 60 days to decide whether to file it so it can bereviewed.

➢ **AbbreviatedNewDrugApplication(ANDA)**

An abbreviated new drug application ANDA contains data which is submitted to FDAfor the review and potentially approval of a generic drug product. Once approved anapplicant may manufacture and market the generic drug product to provide asafe,effective,lower costalternativetothebrandname drugitreferences.

- **Duration**

This act also premises brand name companies to apply for exclusive patient right tocovertheirnewdrugforup to5years.

❖ **ICH-GoodClinicalPractice**

➢ **QualityData+Ethics=GCP(GoodClinicalPractice)**

➢ **GoodClinicalPracticecover thestep**

1. **Design**
2. **Performance**
3. **Monitoring**
4. **Auditing**
5. **Analysis**
6. **Reporting**

➢ **Objective**

FacilitatethemutualacceptanceofclinicaldataacrossICHGCPregion.Avoidtrialduplicationofclinicaldataacross ICHGCPregion. Protectthepatient.
ToProvideauniformstandardfortheEuropeanUnion(EU)JapanUnite.

States to facilitate mural acceptance of clinical data by the authorities in jurisdiction.Avoid duplication (saving time, money , resources). Facilitate global submissionthrough acceptance of data. Technical requirements for medical products containingnew.

➢ **Scope ofGCP**

Good Clinical laboratory should be used in all laboratories where tests are done onbiologicalspecimendiagnosispatientscarefordiseasecannol.

- Microbiologyandserology
- Haematologyandbloodbanking
- Molecularbiologyandmolecularpathology

- Clinicalpathology
- Histopathology

➢ **Keychangesin2019,NewDrugandClinicaltrialsrules**

➢ In new rules 2019,such research has been defined to include studies on basicapplied and operational research or clinical research designed primarily to increasescientific knowledge about disease and conditions, their detection cause andevolving strategies for health promotion, prevention or amelioration of disease andrehabilitationbut doesnotinclude CT.

➢ Thestudytype include:-

- Invitrodiagnosticsperformancetestingforresearch.
- Newsurgicalintervention.
- Assistedreproductivetechnology(ART)
- Publichealthsurvey
- Epidemiologicalhealthsurvey
- Observationalandnon-interventionalstudyofolddrug

➢ **Academicclinicaltrials**

- New rules 2019 described academic clinical trials as clinical trials of a drug alreadyapproved for a certain claim and initiated by any investigators, academic or researchinstitutionsforanewindication ornewdoseornewdosageforms.
- Someimportantpointsforacademicclinicaltrialsinclude.
- Onlyforapproval Drug
- CT initiated by investigators at an academic or research institute can be conductedfor new indication, new route, new dose or dosage forms result only for academic orresearch.
- EC can seek clarity from century licensing authorities and CLA must respond in 30days medicalmanagement.

➢ **EthicsCommittees(ECS)**

- As delineated in the 2019 CT rules and additional resource India has a neutralisedprocess for the ethical review or clinical trials application and requires ethicscommitteeFCapprovalforeachtrialsite.
- Because there is no National EC in the country ECS are based atinstitution/organisation or function independently and must meet the requirements setforthinthe2019CT rulesandtheICME guidelines.
- Ethics committee topic authorising body subtopic for registration requirements is forBCS that over clinical trials is ECS that monitor biomedical and health researchstudiesarealsorequiredtocomplywiththe2019CTrulesandtheFCMRguidelines.

➢ **EC Composition**

- The 2019 CT rules and the ICMR guidelines state that an EC should appoint fromamongmemberhairpeople andamembersecretary.

The other members should represent a balance of affiliated and non affiliatedMedical/nonmedicalandscientific/nonscientificpeoplesincludingthelaypublic.

- As per the 2019 CT rules and the ICMR guidelines preferably 50% of the membersshouldalso benonaffiliatedorfromoutsidethe institution.

➢ **As per the 2019 CT rules and the ICMR guidelines the composition shouldincludethefollowing:**

- Chairpersonfromoutsidetheinstitute
- Onetotwoclinicians fromvariousinstitutions
- Legalexpertsorretiredsudge
- Onephilosopher/ethicist/theologian
- Onelaypersonfromthecommunity
- Member secretary

- Onememberwhoseprimaryareaofinterestisnonscientific
- Represent the scientific patients group as much as possible based on the researcharearequirements.

➢ **PostMarketingSurveillanceStudies**

Such studies are conducted with a new drug under approved conditions of its useandwith scientificobjectives approvedbyCLA.

➢ **Advisedto checkwithCDSCOiftrulyold drug:**

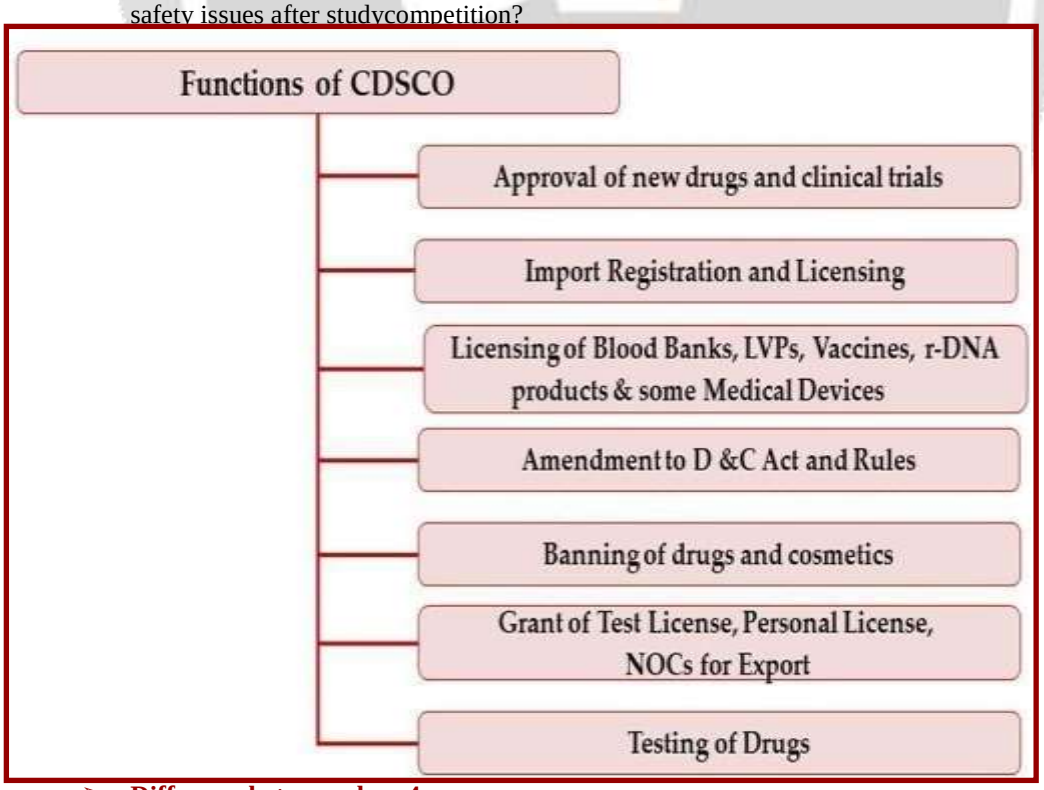
There is an expectation that the number of phase 4 studies being conducted in Indiawill increase. This expectation is based on the assumption that with local clinical trialswaiver a phase4studymightneedtobeconductedexceptinspecialsituations.

➢ **Orphandrugregistration**

- 2019 rules defined orphan drug as a drug intended to treat a condition which defectsnotmorethanfive lakhpeople in India.
- Provision for fast track approval process and special status for orphan drugsincludingacompletefeewaiverforCTfeeling.
- Provisionforexpeditiousreviewprocess.
- Provisionforwaiveroflocalclinicalstudyofphase4onsatisfactionof CLA.

➢ **Posttrialaccess**

- New rules 2019 defined post trial access as marking a new drug or investigationalnew drug available to a trial subject after completion of clinical trials through whichthe said drug has been found beneficial to a trial subject clinical trials for such periodas considered necessary by the investigator and the ethics committee. These drugsshouldbefreeofchargeuponapproval oftheethicscommittee.
- Howlongposttrialaccess of medicineshouldbeprovidedto patients?
- How are safety signals monitored for this period? Should the sponsor/ethicscommittee have responsibilities to record and report safety issues after studycompetition?



➢ **Differencebetweenphase4**

Approved RequiredfromCLA	Approval requiredinincaseofnewdrugandnotincaseofolddrug	
	Phase 4	PMS
Drugtobeprovided	Studydrugtobeprovided	Discriminationofapplicant
Design	As per study protocoldesign	As per prescribinginformation
Compensation	Applicable	Notapplicable
Fees	INR200000(12900)	Notapplicable

Components

1. AdverseEvent CaseManagementIncludingExpeditedReport

- **Fact:-** EU pharmacovigilance laws mean that ALL spontaneous reports regardingserious adverse reactions must be expedited within 15 days. In addition, as of 22ndNovember 2017 all non-serious adverse reactions, with an origin within the EU,requireexpeditingEMAwithin 90 days.
- These laws will mean that ALL suspected reactions provoked by a medicinal productmustbe expedited–regardless ofseriousness.
- **Expeditedreports**

  Remaining compliant throughout all the changes to EU legislation can be achallenging endeavour for any company. This is particularly the case with ExpeditedReporting–oneofthepillars ofall EUpharmacovigilancework.
- **WhatIsExpeditedReporting?**

  In the EU post-marketing environment, an Individual Case Safety Report (ICSR) mayinvolveaserious ornon-seriousadversereaction–regardlessofexpectedness.
  Such cases must be submitted to the regulatory authorities within 15 days or 90 daysrespectively.Asa MarketingAuthorisationHolder,you needtobefullyversed ineach change to the drug safety laws in concerned territories around expeditedreporting as and when it happens. With regards to these updates, you as theMarketingAuthorisationHolderneedtoimplementthemtoremainfullycompliant.
  With the right support, you can rapidly respond to the challenges in line with yourStandardOperatingProcedures.
- **Post-MarketingPhases**

  Any clinical trials including post-authorization studies during the post-marketingphase of a product will need to be correctly processed and expedited according toregulatoryrequirements

2. AggregateReporting

- Aggregate reporting is the process that reviews the cumulative safety informationfrom a wide range of sources, on a periodic basis and submits the findings toregulatorsworldwide.
- Theaggregatesafetyreportsarepresentedtoregulators assoonasthemedicineis marketed anywhere in the world and enables understanding of the risk and benefitprofileoftheproductoveraperiodoftime.
- Thesereportsfocusnotsomuchonindividualcases,butratheronoverview, assessment of the safety profile and benefit-risk-evaluation of Adverse DrugReaction(ADR)andtheSeriousAdverseEvent(SAE)andpregnancyreports.
- **Whyis aggregatereportingimportant?**

  Though the Individual case safety reports were submitted on expedited basis toregulatory authorities, detailed analysis and evaluation of the benefit/risk ratio of adrug is not possible at this level. Therefore periodically reviewing safety
  reportsreceivedcumulativelyworldwide,becomeshighlysignificanttoanalyseth

benefit/riskbalanceoftheproduct.

1. **Post-marketingreport:**

- Periodic Benefit Risk Evaluation Report (PBRER)/Periodic Safety Update Report(PSUR)
- PeriodicAdverseDrugExperienceReport(PADER).
- NDAandANDAannualreports
- Addendumtoclinicaloverviews(ACO).

➢ **Typesofaggregatereports:**

2. **Pre-marketingreport:**

- INDannualreports•Clinicalstudyreports(CSR)
- DevelopmentSafetyUpdateReport(DSUR)
- Annualsafetyreports(ASRS)inEurope

3. **SingleIntelligence**

➢ Signal detection in Pharmacovigilance involves looking at the adverse reaction datafor patterns that suggest new safety information. This page provides a briefintroduction to the definition and purpose of signals and some of the keymethodologiesemployed togeneratethem.

➢ **WhatIsASignal?**

- The term is most commonly associated with drugs during the post-marketing phase,although it may also be used during pre-marketing clinical trials. The definition of asignalasprovided bytheCIOMSWorkingGroup8 is:
- information that arises from one or multiple sources (including observations andexperiments), which suggests a new potentially causal association, or a new aspectof a known association, between an intervention and an event or set of relatedevents, either adverse or beneficial, that is judged to be of sufficient likelihood tojustifyverificatoryaction".

➢ **WhatIsSignalManagementinPharmacovigilance?**

- The process of signal management in pharmacovigilance is a set of activities whichaim todetermine:
- whether there are new risks associated with a particular drug, orwhether risks associated with a particular drug have changedSourcesforthedetectionofsignalscancomefrom:
- spontaneousreporting
- activemonitoringsystems
- interventionalstudies(clinicaltrials)
- non-interventionalstudies(pharmacoepidemiologystudies)
- non-clinicalstudies(e.g.animaltoxicologystudies)
- systematicreviews(i.e.thoroughreviewofthepublishedliterature)
- meta-analyses(i.e.mathematicalpoolingofalltheclinicaltrialdata)
- otherrelevantsources.
- **Definition,Objective,TypesandComponentsofpharmacovigilance**

❖ **Definition**

Pharmacovigilance is the science and activities relating to the detection assessment,understanding and prevention of adverse effects or any other medicine vaccinerelatedproblemsforpatientssafety.

❖ Objective

➢ Improvement of patients Career Safety in relation to the use of medicines withmedicalandparamedicalinterventionsremainstobeanimportantParamet er.

➢ The main objective of Pharmacovigilance involves exhibiting the efficacy of drugs bymonitoring their adverse effect profile for many years from the lab to the pharmacy!improving tracking and drasting effect of drug Improving public health and Safety inrelation to the use of medicines uncovering the safe rational and cost effective use ofdrugs.

➢ Promotingunderstandingedvatioandclinicaltraininginpharmacovigilancean deffectivecommunicationtothegenericpublic.

➢ In addition providing information to the effective use of drugs along designingprograms and procedures for collecting and analysing reports from patients andclinicalconclusions tothe objectiveofpharmacovigilance.

❖ Types

➢ Therearefourimportanttypesinpharmacovigilance:

1. **Passivesurveillance**
2. **Activesurveillance**
3. **Cohorteventmonitoring.**
4. **Targetedclinicalinvestigation**

1. Passivesurveillance

➢ Passive surveillance methods involve the usage of spontaneous adverse eventreports voluntarily sent by healthcare professionals or patients to the marketingauthorization holder or regulatory authority. Here, data related to the adversereactions are collected in a central or regional database. The identity of the reporterremains anonymous, but patient-related details like country, age, gender, and pre-existingcomorbidities canberecoveredfromthereportingforms.

➢ Examplesofspontaneousreporting systemsincludethe-

➢ FAERS (FDA Adverse Event Reporting System) database run by FDAVigiBase™, the WHO Global Individual Case Safety Report (ICSR) databaseForEurope:EudraVigilancemaintainedbytheEuropeanMedicines Agency.

2. Activesurveillance

➢ This method aims to monitor certain specific drug-related adverse events and seeksto ascertain the number of adverse drug reactions entirely through a pre-plannedprocess.Itiscommonlyknownastoxicitymonitoringorsafetymonitoring.

3. cohorteventmonitoring

➢ This method, the surveillance study is planned prior to beginning the treatment withthe medication. A group of people are exposed to a drug for a defined period andactivelyfollowed up during treatment.

➢ Adverseeventsofthetarget drug ortheeventsassociatedwithoneormoremedicinestakenwiththatdrugarem onitored.

4. Targetedclinicalinvestigation

➢ Thesekindsof investigations areperformedtoidentifyandcharacterisetheadverse

reactions related to a drug among special populations like people with some geneticdisorders,pregnantwomen,andolderpeople.

➢ **#PharmacovigilanceProgrammeofIndia(PvPI):-**

The Central Drugs Standard Control Organization (CDSCO), Directorate General ofHealth Services under the aegis of Ministry of Health & Family Welfare, Governmentof India in collaboration with Department of Pharmacology, All India Institute ofMedical Sciences (AIIMS), New Delhi has launched the nation-widePharmacovigilance programme for protecting the health of the patients by ensuringdrug safety. The programme is coordinated by the Department of Pharmacology atAIIMSas a National Coordinating Centre(NCC**).**

4.RiskManagement

➢ Risk management in pharmacovigilance is undertaken to promote safe use ofmedicines and safeguard health of patients. It is a set of activities performed foridentification of risk, risk assessment, and risk minimization and prevention. Riskmanagementhasthefollowingstages:identification andcharacterizationofthesafety profile of the medicinal product; planning of pharmacovigilance activities tocharacterise risks and identify new risks; planning and implementation of riskminimization and mitigation and assessment of the effectiveness of these activities;and document postapproval obligations that have been imposed as a condition of themarketingauthorization.

All these activities together constitute the risk management plan, which is required tobe submitteddurringtheauthorizationofthedrug.Theoverallaimofriskmanagementistoen surethatthebenefitsofthemedicinalproductoutweighthericksbyawidemarginforthetre atmentofaparticularindicationbothat individual

❖ **ObjectiveOF(PvPI):-**

➢ TomonitorAdverseDrugReactions(ADRs)intheIndianpopulation.

➢ To create awareness amongst health care professionals about the importance ofADRreportinginIndia.

➢ Tomonitorbenefit-riskprofileofmedicines

➢ Generateindependent,evidencebasedrecommendationsonthesafetyofmedicines

➢ SupporttheCDSCOforformulatingsafetyrelatedregulatorydecisionsformedicines

➢ Communicatefindingswithallkeystakeholders

➢ Create a national centre of excellence at par with global drug safety monitoringstandards

Listofnationaladversedrugmonitoringcentres(AMCS)andtheirfunctions:

❖ **NationalCoordinatingCentre(NCC):-**

➢ **Address :**-Department of Pharmacology, All India Institute of Medical Sciences,NewDelhi.

➢ **Coordinators:**-Dr.Y.K.GuptaNationalCoordinator

➢ **ADRMonitoringCentres(AMC):-**

Sr.no.	Address	Coordinators
01.	Department ofPharmacology, Therapeutics &Toxicology,Govt.Medical	Dr.VishalTandon

	College, Bakshi Nagar,Jammu.	
02.	Department ofPharmacology, PGIMER,Chandigarh	Dr. BikashMedhi
03.	Departmentof Pharmacology,R.G. KarMedicalCollege,Kolkatta	Dr.AnjanAdhikari
04.	Department ofPharmacology,Lady Hardinge MedicalCollege,NewD elhi	Dr. H.S.Rehan
05.	Department of ClinicalPharmacology,SethG S Medical College & KEMHospital,Parel,Mumbai	Dr.UrmilaThatte
06.	DepartmentofClinical&Expe rimentalPharmacology,Schoo lofTropicalMedicine, Chittaranjan Avenue,Kolkata	Dr. SantanuTripathi
07.	Department ofPharmacology,JIPMER,Po ndicherry	Dr.CAdithan
08.	Department of ClinicalPharmacy,JSSMedical CollegeHospital,Kar nataka	Dr.ParthasarathiG
09.	Department ofPharmacology,MedicalCol lege,Guwahati. Assam	Dr.MangalaLahkar
10.	HimalayanInstituteof Medical Sciences,Dehradun,Uttrak hand	Dr.DCDhasmana
11.	Department of ClinicalPharmacology,Christi an Medical College,Vellore,TamilNadu	Dr. Sujithchandy

❖ **FunctionofAMC**

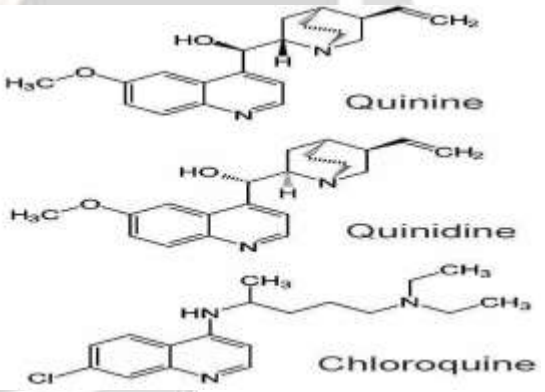
- TomonitortheADR.
- ToOptimisesafeandeffectiveuseofmedicinesinover setup.
- To create awareness amongst healthcare professionals about the importance of ADRReporting.
- Tomonitorbenefitsriskprofileofmedicines.
- Generate independent, evidence based recommendations on the safety ofmedicines.
- SupporttheCDSCOforformulatingsafetyrelatedregulatorydecisionsformedicines.
- Communicatefindingwithallkeystakeholders.
- Create a national centre of excellence as per with global drug safety monitoringstandards.

QuinineDrug

- History
- An alkaloid derived from the bark of the cinchona tree. It is used as an antimalarial drug, andis the active ingredient in extractsof the cinchona that have been used for that purposesince before1633
- Authors
- PierreJosephPelletierAndJosephCaventou
- Summary
- QuinineisanalkaloidusedtotreatuncomplicatedPlasmodiumfalciparummalaria.
- Background
- An alkaloid derived from the bark of the cinchona tree. It is used as an antimalarial drug, andis the active ingredient in extracts of the cinchona that have been used for that purpose sincebefore 1633. Quinine is also a mild antipyretic and analgesic and has been used in commoncold preparations for that purpose. It was used commonly and as a bitter and flavoring agent,and is still useful for the treatment of babesiosis. Quinine is also useful in some musculardisorders, especially nocturnal leg cramps and myotonia congenita, because of its directeffectsonmusclemembraneandsodiumchannels.Themechanismsofitsantimalarialeffectsarenotwellunderstood

.

- BrandNames
- Qualaquin,Quinbisul,etc
- Structure



- Weight
- Average:324.4168
  Monoisotopic:324.183778022
- ChemicalFormula
- $C_{20}H_{24}N_2O_2$
- ProteinBinding
- Approximately70%
- Half-Life
- Approximately18 hours
- ClinicalTrials

PHASE	STATUS	PURPOSE	CONDITIONS	COUNT
4	Completed	Not Available	Plasmodium Infections	1
4	Completed	Basic Science	Obesity	1
4	Completed	Treatment	Anemia	1
4	Completed	Treatment	Plasmodium Infections	2

- Sponsors
  Takeda
- InformationProvidedby
  Takeda

StudyDescription

Since many of the adverse events associated with quinine are dose-related, it is important toconsider how varying degrees of renal dysfunction alter quinine pharmacokinetics possiblywarrantingdosageadjustment in thesepatients.

This study will compare the pharmacokinetics of quinine in patients with normal, mild ormoderate renal impairment. Eighteen non-smoking males and female volunteers between 18-65 years of age weighing at least 60 kg with BMI between 18- 40 kg/m2 will be divided into 3groups of 6 subjects each based on renal function as defined (6 normal, 6 mild impairment, 6moderateimpairment).

Subjects will be confined to the study unit during the entire 5 day study period beginning onthe evening of Day -3. To confirm renal function classification, creatinine clearance will bemeasured via 24-hour urine collection from 7am Day -2 until 7am Day -1. On day 1, after afastofatleast8hours, each patientwillreceiveasingle648mgdoseofquininesulfate.

Blood and urine samples will be collected at times sufficient to adequately define thepharmacokinetics of quinine and its active metabolite, 3'-hydroxyquinine) in the three studygroups.Subjectswillbemonitoredregardingadverseeffectsthroughoutstudyparticipation.

Condition or disease	Intervention/treatment	Phase
Healthy Renal Impairment	Drug: quinine sulfate	Phase 1

StudyDesign

- StudyType : Interventional(ClinicalTrial)
- ActualEnrollment : 5participants
- Allocation Non-Randomized
- InterventionModel ParallelAssignment

- Masking — None(OpenLabel)
- PrimaryPurpose — BasicScience
- OfficialTitle — A Single-Dose, Open-Label Comparative Study of thePharmacokinetics,Safety,andTolerabilityofOralQuinineSulfate in Healthy Volunteers and Adults With Mild andModerateRenal Impairment
- StudyStart Date : November 2007
- Actual Primary CompletionDate : January2011

Armsandintervenation

Arm	Intervention/treatment
Experimental: 1 quinine sulfate 648mg in subjects with normal renal function (CLcr ≥ 80mL/min)	Drug: quinine sulfate 2 x 324mg given in one dose to healthy subjects Other Name: Qualaquin
Experimental: 2 quinine sulfate 648mg in subjects with mildly impaired renal function (CLcr ≥ 50 to 80 mL/min)	Drug: quinine sulfate 2 x 324mg given as one dose to subjects with mild renal impairment Other Name: Qualaquin
Experimental: 3 quinine sulfate 648mg in subjects with moderately impaired renal function (CLcr 30 to 50mL/min)	Drug: quinine sulfate 2 x 324mg given as one dose to subjects with moderate renal impairment Other Name: Qualaquin

- Outcomemeasures

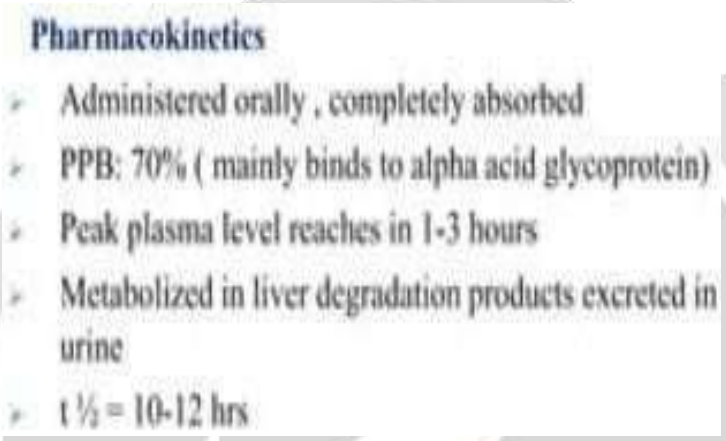
  Primary Outcome Measures : Alterations pharmacokinetic profile of quinine and 3'-hydroxyquinine in plasma (total and free) and urine following a single 648mg dose of quininesulfate in healthy subjects with normal renal function versus those with mild and moderaterenalimpairment[Time Frame: 72hours]

  Secondary Outcome Measures : Differences in safety and tolerability of quinine sulfate inhealthy subjects versus those with mild and moderate renal impairment [Time Frame: up to72hours]

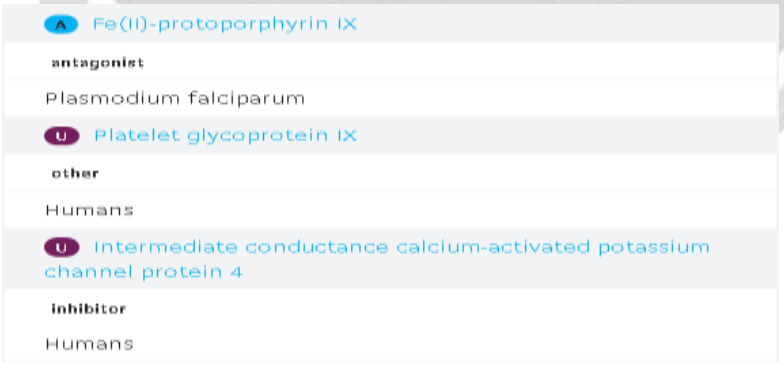
- Pharmacodynamics

  The MIC results in a parasite multiplication rate of 1, and with an unrestrained approximateparasite multiplication rate of 10 per cycle, this is similar to the 90% inhibitory concentration(IC90) valueinvitro(11).

- Pharmacokinetics



- MechanismofActions
- The theorized mechanism of action for quinine and related anti-malarial drugs is that thesedrugs are toxic to the malaria parasite. Specifically, the drugs interfere with the parasite'sability to break down and digest hemoglobin. Consequently, the parasite starves and/orbuildsup toxiclevels ofpartially



degradedhemoglobinin itself.

- Administration
- Undiluted quinine injection is painful when given by IM, so it is therefore best to administer inabufferedformulation or dilutedto60-100mg/mL.

Injectable quinine dosing table (IV)	
Category	**Dose**
Initial dose	20 mg salt/kg bodyweight

- Toxicity

Quinine is a documented causative agent of drug induced thrombocytopenia (DIT).Thrombocytopenia is a low amount of platelets in the blood. Quinine induces production ofantibodies against glycoprotein (GP) Ib-IX complex in the majority of cases of DIT, or morerarely, the platelet-glycoprotein complex GPIIb-IIIa. Increased antibodies against thesecomplexesincreasesplateletclearance,leading totheobservedthrombocytopenia.

DrugInteraction

DRUG	INTERACTION
1,2-Benzodiazepine	The risk or severity of adverse effects can be increased when Quinine is combined with 1,2-Benzodiazepine.
Abametapir	The serum concentration of Quinine can be increased when it is combined with Abametapir.
Abatacept	The metabolism of Quinine can be increased when combined with Abatacept.
Abciximab	The therapeutic efficacy of Abciximab can be increased when used in combination with Quinine.
Abemaciclib	The serum concentration of Abemaciclib can be increased when it is combined with Quinine.
Abiraterone	The serum concentration of Quinine can be increased when it is combined with Abiraterone.
Abrocitinib	The serum concentration of Quinine can be increased when it is combined with Abrocitinib.
Acalabrutinib	The metabolism of Acalabrutinib can be increased when combined with Quinine.
Acarbose	The risk or severity of hypoglycemia can be increased when Acarbose is combined with Quinine.
Acebutolol	The metabolism of Acebutolol can be decreased when combined with Quinine.

- FoodInteraction
- Takewithfood.Foodreducesirritation.

- DrugDisease Interaction
- Quininehasnoknownsevereinteractions withotherdrugs.
- Seriousinteractionsofquinineinclude:
- isapride
- dronedarone
- eliglustat
- pimozide
- thioridazine
- Quininehasserious interactionswithatleast48differentdrugs.
- Quininehasmoderateinteractions withatleast138differentdrugs.
- Quininehasminorinteractionswithatleast82differentdrugs.

- This information does not contain all possible interactions or adverse effects. Therefore,beforeusingthisproduct, tellyourdoctororpharmacistofalltheproductsyouuse.

Genotoxicty

- Quinine,termeda"generalprotoplasmicpoison"istoxictomany bacteria, yeasts, andtrypanosomes, as well as to malarial plasmodia. Quinine has local anesthetic action but also isan irritant. The irritant effects may be responsible in part for the nausea associated with itsclinicaluse.

- EfficacyofDrug

- All 217 patients with efficacy outcomes were included in the analysis. No ETF was detected(Table 2). Almost 70% (74/110) of children in the quinine arm had a recurrent infection ascompared to 60% (21/35) in the AL and 25% (18/72) in the DHAPQ arms (Table 2). Bothquinine(HR=3.9;95%CI:2.4–6.7)(p<0.0001)andAL(HR=3.3;95%CI:1.8–6.3)(p<0.0002)hada significantly higher risk of recurrent infection as compared to DHAPQ (Table 3). Nosignificant difference in recurrent infection was found between quinine and AL (p=0.4) (Table3). Most recurrent infections were identified as new infections. Though the PCR-adjustedtreatment failure tended to be lower in the DHAPQ (1%, 1/72) than in the quinine (7%, 8/110)and AL (6 %, 2/35) groups, it did not reach statistical significance (Table 3). Thee rate ofrecurrent infections was lower and occurred later in the DHAPQ treatment group (Figure 3).Thebaselineparasitedensityandtreatmentallocationforthe primarymalariaepisodehadno influenceontreatmentoutco

k category	28 day risk of treatment failure, % (95% Confidence Interval)	Hazard Ratio (95% CI)	p-value
Unadjusted by genotyping			
ine vs AL	667 (590-750) vs 600 (430-760)	1·23 (0·78-2·00)	0·398
uinine vs DHAPQ	667 (590-750) vs 250 (150-350)	3·98 (2·37-6·68)	<0·0001
s DHAPQ	600 (430-760) vs 250 (150-350)	3·32 (1·76-6·26)	0·0002
Adjusted by genotyping.			
ine vs AL	70 (20-120) vs 60 (01-120)	1·30 (0·27-6·22)	0·739
uinine vs DHAPQ	70 (20-120) vs 10 (01-40)	2·09 (0·25-17·43)	0·497
s DHAPQ	60 (01-120) vs 10 (01-40)	1·62 (0·14-18·31)	0·697

sodes with no outcomes and recurrent parasitemia/malaria caused by non-falciparum species censored.

eatment outcomes	Treatment group[a]		
	Quinine (n = 111)	AL (n = 35)	DHAPQ (n = 72)
to follow-up /no treatment outcome)1		0	0
Early treatment failure (ETF)	0	0	0
e clinical failure (LCF)	31 (28%)	7 (20%)	6 (8%)
Late parasitological failure (LPF)	43 (39%)	14 (40%)	12 (17%)
quate clinical and parasitological onse (ACPR)	36 (33%)	14 (40%)	54 (75%)
All failures			
rall	74 (67%)	21 (60%)	18 (25%)
New infection	62 (56%)	16 (46%)	15 (21%)
rudescence	8 (7%)	2 (6%)	1 (1%)
Genotyping unsuccessful	4 (4%)	3 (9%)	2 (3%)

= Artemether- lumefantrine, DHAPQ = Dihydroartemisinin piperaquine.

CommonSideEffect

- flushingoftheskin
- chestpain
- fever
- rash
- itching
- low bloodsugar

Uses

Quinine is used to treat malaria caused by Plasmodium falciparum. Plasmodium falciparum isa parasite that gets into the red blood cells in the body and causes malaria. Quinine works bykillingtheparasiteorpreventing itfromgrowing.

PostMarketingMonitoring

The report covers forecast and analysis for the quinine market on a global and

regional level.The study provides historic data from 2015 to 2018 along with a forecast from 2019 to 2025based on revenue (USD Million). The study includes drivers and restraints for the quininemarket along with the impact they have on the demand over the forecast period.Additionally, the report includes the study of opportunities and various trends in the quininemarketonagloballevel.

- *As per the report, the global demand for quinine market was valued at approximately USD804.98millionin2018andisexpectedtogeneraterevenueofaroundUSD1,184.15millionbyendof2025,growingataCAGRofaround5.68%between2019and2025.*

- Based on mode of administration, the quinine market is segmented into oral administration,intravenous administration, intramuscular administration and others. Among the mode ofadministration segment, intramuscular segment is most commonly used mode ofadministration. Based on the application, the market is classified into antimalarial, antipyreticand others. The most dominant application segment is anti-malarial application in terms ofrevenue.

- End user segment of quinine market is further divided into hospitals, clinics, ambulatorysurgery centers, and others. Hospitals application segment dominated the market in terms ofrevenuein2018 owingtomore inclinationofpatientstowardsthehospitals.

- Geographically, in 2017, the Middle East and Africa dominated the quinine industry and willcontinue to develop considerably over the forecast period. High production cinchona, anincreasing incidence of malaria, and an increasing amount of fever cases will cascade thedevelopmentofthesectorovertheforecastperiod.
- Asia Pacific is anticipated to closely follow the trend. Asia Pacific is anticipated to see thegreatest development during the forecast period as a result of rising healthcare spending,rising disposable revenue leading to increased affordability, and increasing patient tendencytowards quinine derivatives. High population base in India, improved patient knowledge ofmalaria, andincreasedfevercausingdiseaseswillfurtherincreasemarketgrowth.

- Some of the key players in quinine market include Alchem International, Van WankumIngredients, Arnold Suhr Qimpex, Vital Labs, Cosmos International, Chempro Pharma PrivateLimited, amongothers.

- Selection of a drug class for pharmacovigilance study using different criteria (e.g commercialavailability,sellingof drugetc).

- AVAILABILTY

- Quinineisaprescriptiondrugusedasanantimalarialdrugindicated onlyfor

- the treatmentof uncomplicated*Plasmodiumfalciparummalaria*.

- Quinine sulfate has been shown to be effective in geographical regions where resistancetochloroquinehasbeendocumented.

- Quinineisavailableunderthefollowingdifferentbrandnames:Qualaquin.

- DosageofQuinine:

- Adult and Pediatric DosagesCapsule

  324 mg

- **DosageConsiderations–ShouldbeGivenasFollows**:

- **Malaria**

- Adults

- Uncomplicated(*P.falciparum*)

  648mg orallyevery8hoursfor7days

- Chloroquine-Resistant(*P.falciparum*)

  648 mg orally every 8 hours for 3-7 days concomitanttetracycline,doxycycline,orclindamycin

- Chloroquine-Resistant(*P.vivax*)

648 mg orally every 8 hours for 3-7 days concomitant doxycycline (or tetracycline)andoralprimaquine

- Pediatric DosagesUncomplicated(*P.falciparum*)

  30 mg/kg/day orally divided three times daily for 3-7 daysShouldnotexceedtheusual adultoraldosage

- Chloroquine-Resistant(*P.falciparum*)

  30 mg/kg/day orally divided three times daily for 3-7 days, with concomitantdoxycycline,tetracycline,orclindamycin Shouldnotexceedtheusualadultoraldosage

- Chloroquine-Resistant(*P.vivax*)

  30 mg/kg/day orally three times daily for 3-7 days, with concomitant doxycycline andoral primaquine Shouldnotexceedtheusualadultoraldosage

- **Babesiosis**

- AdultDosage:

  648mgorallyevery8hours,withconcomitantorallyor intravenouslyclindamycin

- PediatricDosage:

  25 mg/kg/day orally divided three times daily for 7 days, with concomitant oralclindamycin

- DosageModifications

  Severe, chronicrenalimpairment:648mgorallyonce,then324mgorally every12hours

- Hepaticimpairment

Mildormoderate(Child-PughAorB):Nodosageadjustmentrequired;monitorclosely

Severe(Child-PughC):Donotadminister

- SELLINGOFDRUG
- Drugclass:Quinineisinaclassofmedicationscalledantimalarials
- Drugform:Quininecanalsobeadministeredviaintramuscularinjectionifintravenousinfusions cannot be given: two injections of 10 mg salt/kg quinine dihydrochloride (diluted to60mL)shouldbeadministeredfourhoursapart.Theanteriorthighispreferredoverthegl utealregiontominimizetheriskofsciatic nervedamage.
- BrandNameversion:Qualaquin
- USINGAMAILORDERPHARMACY
- Quinine may be available through a mail-order pharmacy. Using this type of service may helplower the drug's cost and allow you to receive your medication without leaving home. SomeMedicareplansmayhelpcoverthecostofmail-ordermedications.Youmayalsobeabletogeta 90-day supply of the drug via mail order. If you don't have health insurance, talk with yourdoctor or pharmacist. They may be able to suggest online pharmacy options that could workforyou.
- Financialandinsuranceassistance
- If you need financial support to pay for pantoprazole, consider looking into websites that offercostresourcesandinformation.TwosuchorganisationsareMedicineAssistanceToolNeedyMeds These sites can provide details on drug assistance programs, ways to make themostofyour insurancecoverage, andlinkstosavingscardsandotherservices
- Nextsteps
- Nowthatyou'velearnedaboutcostandpantoprazole,youmaystillhavesomequestions.Talkwith your doctor or pharmacist, who can provide personalised guidance on cost issues relatedto you and pantoprazole. If you have health insurance, you'll need to talk with your insuranceprovider to learntheactualcostyouwouldpayforpantoprazole.
- Medicare drug coverage: To learn about Medicare coverage for drugs, see these articles onMedicarePrescriptionDrugPlans,drugcouponsandMedicare, andtheMedicaredruglist.
- Savemoney:Explorethisarticlefortipsonhowtosavemoneyonprescriptions.

- Moredetails:Fordetailsaboutotheraspectsofpantoprazole,refertothisarticle.

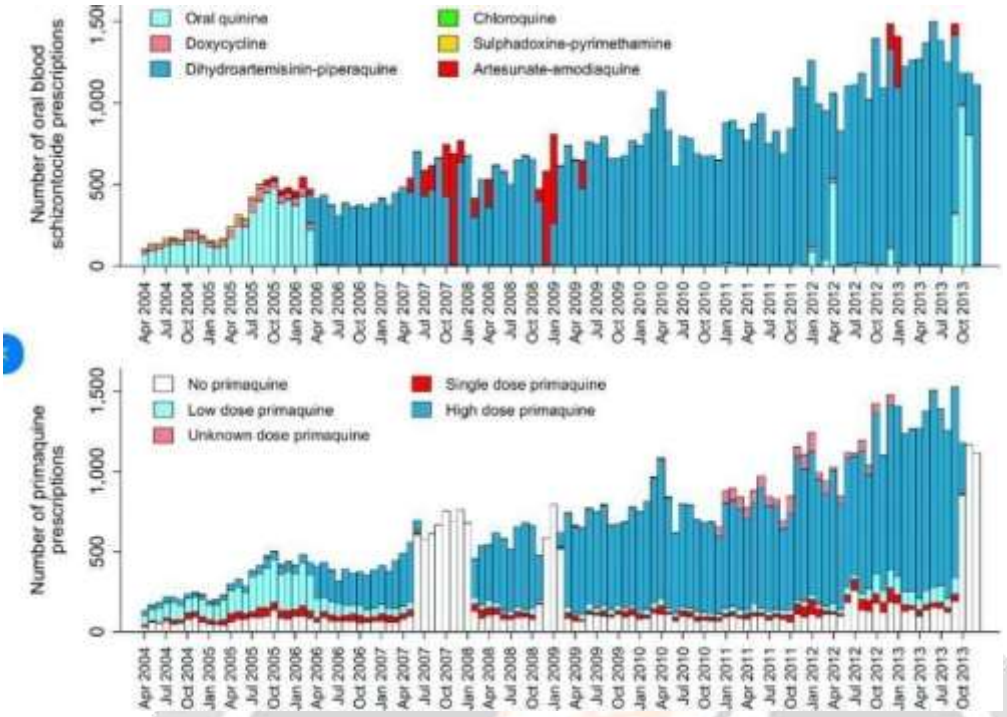
- Informationonyourcondition:Formoreinformationabouttheconditionspantoprazoleis usedtotreat, thislistofarticles related to thegastrointestinal systemmaybehelpful.

- Disclaimer: Medical News Today has made every effort to make certain that all information isfactually correct, comprehensive, and up to date. However, this article should not be used as asubstitute for the knowledge and expertise of a licensed healthcare professional. You shouldalways consult your doctor or another healthcare professional before taking any medication.The drug information contained herein is subject to change and is not intended to cover allpossible uses, directions, 10 11 precautions, warnings, drug interactions, allergic reactions, oradverse effects. The absence of warnings or other information for a given drug does notindicate that the drug or drug combination is safe, effective, or appropriate for all patients orallspecific uses.
- Identificationofthemostwidelyprescribeddrugfromaselectedclass(consumptionrepor t)byapproachingpharmacystorescompanyrepresentationandPharmacompanieswebpo rtals.

- CONSUMPTIONREPORT

- Based on region, the market is segmented into North America, Europe, Asia Pacific, LatinAmerica and Middle East & Africa (MEA). North America region is further bifurcated intocountries such as U.S., and Canada. The Europe region is further categorized into U.K., France,Germany, Italy, Spain, Russia, and Rest of Europe. Asia Pacific is further segmented into China,Japan, South Korea, India, Australia, South East Asia, and Rest of Asia Pacific. Latin Americaregionisfurthersegmentedinto Brazil,Mexico,andRestofLatinAmerica,andth eMEAregionisfurtherdividedintoGCC,Turkey,SouthAfrica,andRestofMEA.

- TotalPresciptionAndPatientPerYear


Number of oral blood schizontocide prescriptions
Oral quinine
Doxycycline
Dihydroartemisinin-piperaquine
Chloroquine
Sulphadoxine-pyrimethamine
Artesunate-amodiaquine
0
500
1,000
1,500
Apr 2004
Jul 2004
Oct 2004
Jan 2005
Apr 2005
Jul 2005
Oct 2005
Jan 2006
Apr 2006
Jul 2006
Oct 2006
Jan 2007
Apr 2007
Jul 2007
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Apr 2010
Jul 2010
Oct 2010
Jan 2011
Apr 2011
Jul 2011
Oct 2011
Jan 2012
Apr 2012
Jul 2012
Oct 2012
Jan 2013
Apr 2013
Jul 2013
Oct 2013
Number of primaquine prescriptions
No primaquine
Low dose primaquine
Unknown dose primaquine
Single dose primaquine
High dose primaquine

- RankofTopdrugsovertime

- "Rank" refers to the frequency that a given medication is prescribed within a calendar yearcompared to all other medications. A rank of "4" would indicate that the medication was thefourthmostcommonlyprescribedmedication.

- DrugCostOverTime

- *Cost Per Prescription Fill*: Average cost per filled prescription regardless of how many days oftherapy theprescriptionisfilled for(e.g.10days,30days,90days,etc.)

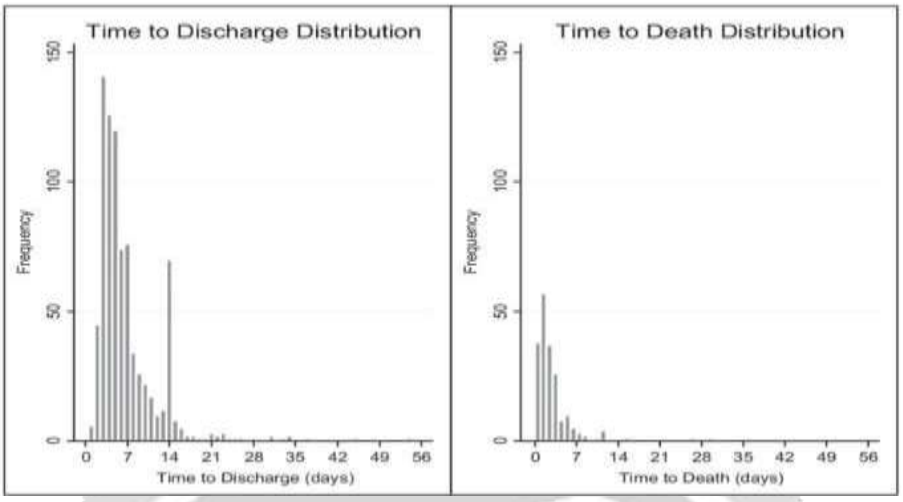
- *Cost per Day of Therapy*: The average cost per prescription fill divided by the days of therapy.For example, a 10-day antimalarial course costing $30 would be $3 per day. Similarly, a 30-daysupply ofanoralantihypertensivecosting$30wouldbe$1perday.

- *Total cost:* The average total cost of the medication including the out-of-pocket cost (seebelow)plustheamountpaidbyotherparties(Medicare,Medicaid,privateinsurance, VeteransAdministration,TRICARE,otherstate/federalsources,Worker'scompensation,andothermiscellaneoussources)

- *Out-of-pocket cost*: The average payment made by the patient which may include deductibles,coinsurance, copayments,orthecashpricepaidwithoutinsurancecoverage.

- CostperPrescription

- DistributionofDayssupplied



- TherapeuticClasses

- Drugsynonyms

- Drug synonyms are used during the sanitation and standardisation process of "cleaning" theoriginaldatasource(MEPS).Occasionally,brandnamesmaybelistedbelowthatarenolongeronthemarketorare veryinfrequentlyused

- Brandnamesynonyms

- Qualaquin

- Quinbisul

- GenericDrugSynonymsandSalts

- QuinineSulphate

- FDAApprovalInformation

- FDA has ordered all firms to cease manufacturing unapproved products containing quinine,including quinine sulfate and any other salt of quinine on or after February 13, 2007, and tocease shipping such products interstate on or after June 13, 2007. After these dates only FDAapprovedquinineproductsmaybemanufacturedandshippedinterstate.Thisactionisdescribedin theFederalRegister ofDecember15,2006,[71FR75557].

Identification of adverse effects of a selected drug using different searchengines(e.g-Medscape.com,drug.com,rxlist.com,etc)

- **Adverseeffects(Medscape.com)**

<1%

- Flushingoftheskin
- Anginalsymptoms
- Fever
- Rash
- Pruritus
- Hypoglycemia
- Epigastricpain
- HemolysisinG6PDdeficiency
- Thrombocytopenia

- **Adverseeffects(drugs.com)**
- Blurredvision
- changeincolorvision
- changesinbehavior
- confusion
- diarrhea
- hearing loss
- nausea
- ringingintheears

- **Adverseeffects(rxlist.com)**
- **Commonsideeffectsofquinineinclude:**
- **Fever**
- **Chills**
- **Sweating**
- **Flushing**
- **asthenia**
- **lupus-likesyndrome**
- **hypersensitivityreactions.**

Othersideeffectsofquinineinclude:

- bleedingdisorder

- severemalaria(blackwaterfever)
- lowwhite bloodcellcountr
- eductionofredandwhitebloodcells andplateletsintheblood
- nogenerationofnewbloodcells
- lupusanticoagulant
- confusion
- alteredmentalstatus
- seizures
- coma
- disorientation
- shakiness

Postmarketingsideeffects ofquininereportedinclude:

- atrioventricularblock
- irregular,fastheartrate
- extraabnormalheartbeats(unifocalprematureventricularcontractions[PVCs])
- delayedheartbeat
- Uwaves(smalldeflectiononECG)
- seriousirregularheartrhythms(QTprolongation)
- ventricularfibrillation
- torsadesdepointes
- cardiacarrest
- irritationofthestomach
- irritationoftheesophagus
- granulomatoushepatitis
- yellowingof eyesandskin(jaundice)
- abnormalliverfunctiontests
- lossofappetite
- musclepain
- muscleweakness
- bloodintheurine
- kidneyfailure
- kidneyimpairment
- acutekidneyinflammation
- visualdisturbances
- suddenvisionloss
- lightsensitivity
- diminishedvisualfields
- fixeddilatedpupils
- inflammationoftheopticnerve

➢ **Adversedrugreactions**

➢

Indian pharmacopoeiacommission	ForAMCNCCUseonly
A-patient'sinformation;	**AMCreportno:**
1.patientinitial	**Worldwideunique no:**
2.ageattimeevent	**12 .Relevant test laboratory data withdates**
3.M •F. •Other	**13. Relevant medical medication historyE.g-PregnancyAllergy**
4.weight-. Kgs	**14.Seriousnessofreactions** **• Yes-. •No-**
B-suspectedadversereactions:	**•Death-. •Congenitalanomaly-**
5.Dateofreactionsstore	**•Lifethreatening-. •Otherspecific-**
6.Dateofrecovery	**•Disability-**
7.Describereactionorproblem	**•Recovered-. •Recoveringunknown**

❖ **C-suspectedmedication:**

❖ Sr. no	Name(Brand)Generic	Manufa-cturer	Batch No	ExpDate	DoseUsed	Freque-ncy	Route Used	Indicati-on
1.								
2.								
3.								

Actiontaken(pleasetick)	Reactionsreappeared
Drug withdrawal dose increase doseDecrease	•Yes-. •No-. •Effectunknown

❖ **Comitant medical product including self herbal remedies with therapy date(Excludethose usedtousetreatment)**

•Additionalinformation	0.Reporterdetails 16. Name&professionaladdress •pin-. •Email- (Telno). (WithSTD code) •occupation- •Signature- 17. Dateofthisreport

Reference

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7) https://www.medindia.net/patientinfo/pharmacovigilance-the-key-to-drug-safety.htm
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11) https://drvasantraopawarmedicalcollege.com/pvpi-adverse-drug-reactio n-monitoring-centre-amc/
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17) https://pubmed.ncbi.nlm.nih.gov/12973372/
18) https://www.medicalnewstoday.com/articles/drugs-pantoprazole-cost
19) https://clincalc.com/DrugStats/Drugs/Pantoprazole
20) https://reference.medscape.com/drug/amitiza-lubiprostone-342076#4
21) https://www.drugs.com/pantoprazole.html
22) https://www.rxlist.com/consumer_pantoprazole_protonix/drugs-condition.html