# *study of azithromycin drug related with pharmaCovigilance*

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**Abstract**

*Pharmacovigilance is defined by the world health organization as "The Science and activities relating to the detection, assessment, understanding and prevention of the adverse effects or any other drugs related problems. It plays a key role in ensuring that patient receive safe drugs. Pharmacovigilance support safe and appreciate use of drugs. Spontaneous reporting of adverse drug reactions (ADRs) in an essential component of pharmacovigilance. Pharmacovigilance play an important role in health care system through monitoring and interaction of drug and there effect in human body.*

*As pharmacovigilance is concerned with toxicology study of. this study deals with the account of azithromycin(antibiotics) . this review or article paper summaries with all data collected about toxicology and account of azithromycin*

*Keywords- pharmacovigilance, clinical trials, pharmacokinetics, toxicology, adverse drug reactions, reporting.*

*Introduction- Drugs have changed the way in which diseases are treated. Despite all the advantages of pharmacotherapy, adverse reactions are a recognized hazard of drug therapy. Adverse drug reactions (ADRs) are a common, frequently preventable cause of illness, disability and death. An ADR may be defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product". Pharmacovigilance has been described as "the science and activities relating to the detection, assessment, understanding and prevention of the adverse effects of drugs or any other possible drug-related problems. It is a fundamental component of effective drug regulation systems, public health programmes and clinical practice.*

*Clinical trials are prospective biomedical or behavioral research studies on human participants designed to answer specific questions about biomedical or behavioral interventions, including new treatments and known interventions that warrant further study and comparison.*

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❖ Definition and phases of clinical trial:-

**Definition -**

Clinical trial is a prospective ethically designed investigation in *drug* human subject to objectively discover/verify/compare the result of two or more therapeutic measure (drug).

**Types:**

- Pre-clinical trials
- Clinical trials

**Pre-clinical trials**-

After synthesizing/identifying a prospective compound, it is tested on animal to expo se the whole pharmacological profile. Experiment are generally perform on a rodent (mouse, rats guinea pig) rabbit etc and then on a larger animal (cat, dog, monkey)

**following types of tests are performed**:-

**1.Screening test-**

These are simple and rapidly performed. Fest to indicate presence or absence of the particular pharmacodynamics activity that a sought for e.g. - analgesic or hypoglycaemic activity.

**2.Test on isolated organ, bacterial alters etc.-**

These also are pre-luminary test to detect Specific activity such as antihistaminic, anti-secretory, Vasodilator, anti-bacterial etc.

**3.test on animal models of Human disease-**
Such as kindled Seizures in rat, Sponthlneously genetically hypertensive rat experimental tuberculosis in mouse alloxan Induced diabetes in rat or dog etc.
**4.Confirmatory tests and analogous activities-**
Compound found active are taken up for detail study by more elaborate test which Confirm and characterized the activity. other related activities e.g. -antibiotics.
**5.systemic pharmacology**-
Irrespective of the primary action of chug its effect on major organ system such as nervous, cardiovascular, respiratory, renal, GIT are worked out. mechanism of action including additional mechanism e.g. calcium channel blocker adrenergic blockade nitro-Vasodilatation etc.
**6.Quantitative tests** -
The dose response relationship. maximal effect and comparative potency/efficacy with existing drug in ascertained.
**7.pharmacokinetics** –
The absorption, Volume of distribution, metabolism, excretion, patter of tissue distribution and plasma half life Of the drug are quantified.
**8.Toxicity tests**-
The aim is to determine safety of the compound in at least animal one rodent and one nonrodent e.g. -mouse/ rat and dog by oral and parenteral route.

**Types of toxicity**
**1.Acute toxicity** –
Single escalating dose are "given to small group of Animal that are observed for overt effect and mortality for 1-3 days. The dose which kill 50% Animal (LDSO) is calculated. Organ toxicity is examined by histopathology on all animals.
**2.Subacute toxicity**-
Repeated dose are given for 2-12 week depending on the duration of intended treatment in man. dose are selected on the Basis of EDSO and DSO. Animal once examine for over the effect, Food Intake body weight Haematology etc.and organ toxin.
**3.Chronic toxicity**-
The drug is given for 6-12 months and effect are studied as a sub acute toxicity. These is generally Under taken with clinical trials.
**Clinical trials**-
when a compound reserving trial in man is identified by animal studies. The regulatory authorities are approaches who an satisfaction tissue e investigational New drug (IND) linear license.
standards for design, ethics, conduct, mentoring auditing, recording &analyzing. data reporting of clinical trial in the form OF "(Good clinical practice) GLP guidelines. by an International conference of Harmonization (ICH).
The national agencies in most countries including ICMR (Indian council of medical research) In India it is also formed by ethical guidelines for clinical trials.

**clinical trial studies are divided into 4 phase**:-
**1.Phase O- Microdosing study**
The microdosing Human study Under take before phase I trials is also called as phase study.
Very low dose about 1/100 of the estimation Human dose & maxim kium 100ug.
The phase o is studied that the micro dose pharmacokinetic may be different form that at pharmacological doses.
**2)Phase I- Human pharmacology and safety**
The First Human administration of the drug is carried out by clinical pharmacology and trained physician in a sitting where all Vital function and emergency resuscitative facilities are available lowest estimated dose (1/100 to 1/10) of the highest dose producing no toxicity in Animal.
The importance / emphasis in an safety tolerability & function. Heart rate Branchopasm and kidney / liver damage. The side effect is noted & the Pharmacodynamic effect in man.
**3)Phase II - Therapeutic exploration and dose ranging**
This is conducted by physicians When trained as clinical investigators & involve 100-500 patients selected according to Specific inclusion and exclusion criteria.
It is generally carried out at 2-4 Centers.
Phase II is study mostly controlled and randomized.
**4)Phase III- Therapeutic confirmation/comparison**

The aim is to established the Value of the drug in the relation to existing therapy. - Indication are finalised & Guidlines. the therapeutic use for formulated. a NDA is Submitted license authority. (FDA) & convinced to give marketing permission.

**5)Phase IV- post marketing surveillance data gathering Studies**

The drug has been marketed for general Use practising physician are identified data or collection on Structured about efficacy acceptability of efficacy,acceptability, ADR etc.Further therapeutic trials like children, pregnant women patient with hepatic disease etc.Most drug continue then development even after making.

**Function of drug controller General of India (DCGI)-**

- The primary drug authority in india is called CDSCO.
- The organization is in charge of approving licences for specific drug categories.Its main office is in new delhi.
- Under CDSCO ,there are six operational central drug testing laboratories.
- The DCGI is also sets requirement for the production,marketing,import,and distribution of medicines in india
- DCGO is a responsible for Approval of new drug medical device and clinical trials to be conducted in India.
- The DCGI is advisory by the drug technically Advisory Board (DTAB) and drug consultative committee.
- Drug controller general of India is responsible for Approval of license of specified. categories of drug such as blood & blood product I.V fluids and Vaccine and sera.

**function of drug controller General of India (DCGI)** :-

- DCGO is a responsible for Approval of new drug medical device and clinical trials to be conducted in India.
- He is Appointed by the central Govt. Under the DCGI the state drug control organisation will be functioning.
- The DCGI is advisory by the drug technically Advisory Board (DTAB) and drug consultative committee.
- Drug controller general of India is responsible for Approval of license of specified. categories of drug such as blood & blood product I.V fluids and Vaccine and sera.

**function of central drug standard controller general of India (CDSCO)** :-

- Approval of new drug and clinical trials.
- Import registration & licensing.
- Testing of new drugs.
- Grant of test license personal license, 100 for export
- Banning of drug & cosmetics.
- License approving of Vaccines R-DNA product.

**Types of regulatory application**-

**1)Investigational new drug(IND)-** current federal new requires that a drug be the subject of an approved marketing application before it is transported or distributed across state line.

- **Preclinical testing –**

Consist of animal pharmacology & toxicology studies to across whether the safe for testing in human'

- **Manufacturing information** –it include composition ,manufacture and stability of the control used for manufacturing of drug.
- **Clinical trial protocol**-the protocols for proposed clinical studies to initial phase will expose the subject to unnecessary risks.

**2)New drug application –** for the regulation and control of new drug in United States is based on new drug application( NDA).

Since 1938 , every drug has been the subject of approved NDA before U.S commercialization

The goal of NDA are to provide information to permit FDA reviewer

- the drug is safe and effective in its use
- Whether the drug proposed labeling is appropriate and what it should contain
- Whether the method used in manufacturing the drug and the control used to maintain drug purity strength and quality.

The documentation required is an NDA is to tell the drug whole story including what happened during the clinical trials, what the ingredients of drug are results of the Animal studies, how the drug behaves in the body and how it is manufactured, processed and packaged.

**3)Abbreviated new drug application (ANDA)-**

- An abbreviated new drug application ( ANDA) contain data which is submitted to FDA for the Review and potential approval of generic drug product.
- An abbreviated new drug application ( ANDA) is an application for a U.S generic drug approval for an exciting licensed medication or approved drug.
- The ANDA is submitted to FDA centre for drug evaluation and research, office of generic drug which provide the review and approval of generic drug product.
- A generic drug product is one of that is comparable to a patented drug product in dosage form, strength, route of administration, quality and intended use.

**Objective-**

- Protect the patient
- Facilitate the matual acceptance of clinical data across ICH GCP region.
- Avoid trial duplication (saving money,time)
- Facilitate global submission through matual acceptance of data.
- Technical requirements for medicinal products containing new
- Describe the principal of GCP
- Collect the information of GCP guidelines
- To recognise the implication of non-complication.
- To study the concept of informed consent.
- To discuss the key aspects of GCP such as patient requirements consent and Data privacy.

**Scope-**

- Good clinical practice (GCP)- A standard for the design,conduct , performance, monitoring, Auditing, recording analysis and reporting result are credible and accurate and that right,integrity and confidentiality of trials subject are protected.

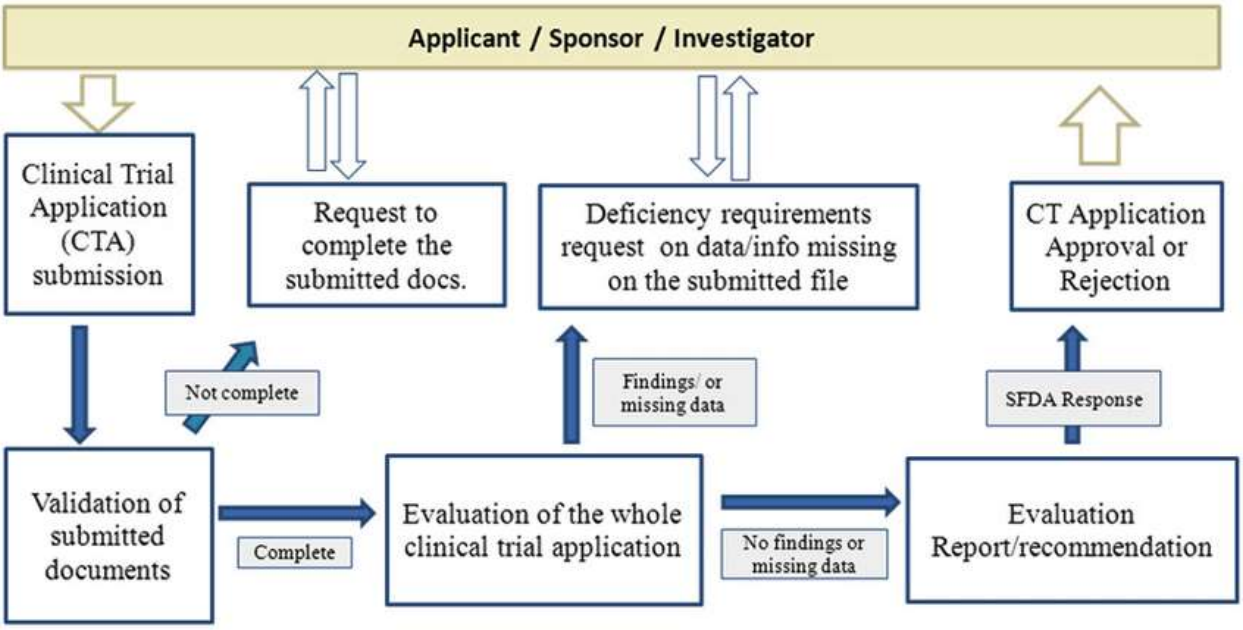
- The objective Of this guidelines the outline of the mission and the organisation of a sponsor auditing department and the principal for planning, performance and reporting audit,all of the which should be considered when the auditor who belong to the sponsor performs an audit a clinical trials performed by the sponsor.

- This guidelines is expected to be a basic principles along with international conference on Harmonization (ICH) good clinical practice (GCP) for a sponsor auditor to conductance audit in the various situation of each country and sponsor.

**Protocol designing for clinical trials-**

- General and background information
- Trial design
- Objective and justification
- Ethical considerations
- Selection and withdraw to subject
- Treatment/study design
- Safety assessments
- Quality control
- Data handling and management
- Finance and insurance
- Evaluation policy
- Supplementories and appendices

**Clinical trials application process (CTA)**-A Clinical Trials Application (CTA) is the application/submission to the competent National. Regulatory Authority for authorization to conduct a clinical trial in a specific country.




**Definition, objective, type and components of pharmacovigilance**:-

**Definition -**

Pharmakon (Greek)-medicinal substance

Vigilia (latin)-To keep watch

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drugs related problems.

**Objective –**

- Improve patient care and safety
- Detection of the increase in frequency of (known) adverse reactions
- Improve safety and public health
- Promote understanding, education clinical training in pharmacovigilance
- Identification of risk factors and possible mechanism of underlying adverse reaction
- The rationale and safe use of drug

**Type and component of pharmacovigilance-**

There are four important method of pharmacovigilance:-

1)Passive surveillance

2)Active surveillance

3)Cohort surveillance

4)Targeted clinical investigation

**1)Passive surveillance-**

- It involves the usage of spontaneous adverse event reports voluntarily sent by healthcare professional or patience to the marketing Authorization holder or regulatory.
- Here date related to the adverse reaction are the collected in central or regional database.
- The identification of the reporter remains anonymous but patient related details like country, gender, age and pre-existing comorbidities can be recovered from the reporting forms.

**2)Active surveillance** –

- This method is aimed to monitor certain specific drug related adverse event and seek to ascertain the number of adverse drug reactions entirety through a pre- planned process.it is also known as toxicity monitoring or safety monitoring.

**3)Cohort event monitoring** –

- In this method the surveillance study is the planned prior to beginning the treatment with medication.
- A group of people are exposed in to the drug for a definite period and actively followed up during treatment.

- Adverse event of target of drug or event associated with one or more medication taken with that drug are monitored.

**4)Targeted clinical investigation** –

- This type of investigation are performed to identify and characterized to the adverse reaction related to the drug among special populations like people with some genetic , pregnant women and oldest person.

**Components of Pharmacovigilance-**

Adverse event case management including

1)Expedited reporting
2)Aggregate reporting
3)Signal intelligence
4)Risk management

**1)Expedited report-**

- Adverse event is any upward medical medical occurance in the patient administration a medical products which does not necessarily have a casual relationship with this treatment.
- An adverse event can therefore be any unfavorable of unintended sign (eg-an abnormal laboratory findings) symptoms or disease temporarily associated with the used of the medical products or not considered related to this medical products.

**2)Aggregate reporting –**

- Aggregate reporting refers to report that the focus not so much on individuals cases but rather on the overview assessment of the safety profile of the benefits risk evaluation.
- E.g. Periodic safety update report (PSUR)/ periodic benefit risk evaluation report (PBRER)
- Periodic adverse (drug) experience report (US).
- development safety update research (DSURS).
- integrated summaries of safety (US)
- clinical summaries to safety or safety related part of clinical studies.

**3)Signal intelligence**

- PV signal intelligence practice are focused on adopting DPA algorithms SRS data for constituting hypothes of signal drug AE combination that needed further investigation to establish evidence based medicine to confirm casualties associating between those pair. These regulatory action may be there taken to protect the public health.

**4)Risk management –**A risk management plan (RMP)provides data on a medicines safety profile,describes the activities of the selling authorization holder to any characterize the safety profile throughout post marketing (Pharmacovigilance activities),and explain the measure that taken in order to avoid or minimize the medicines risk in patients.

**Constitution-**

PV mainly involve monitoring of reports of ADR associated with Use of medicinal products.Under reposting of ADR is a serious issue Hampering of dynamics Of PV .PV is a shared responsibilities of all Stake Holders.

**List of Adverse drug monitoring centres (AMC) & their function-**

1)National Co-ordinating centre (NCC) –

Dept of pharmacology all India Institute of medical science, new Delhi**,**ADR monitoring centre (N

2)Therapeutics & toxicology gost medical collage,Bakshi nagar. Jammu
3)dept of Pharmacology PGIMER, chandigarh
4)RG kar medical collage, Kolkatta
5)lady Hardingo medical collage, new delhi
6)Seth G.S medical collage & KEM Hospital,Parel mumbai.
7)School of tropical medicine chittaranjan.Avenue, kolkata.
8)JIPMER Pondicherry
9)Jss medical collage Hospital, karnataka. Medical college guwahati Assam
10)Madras medical collage, Chennai
11)SAINS medical collage,Ujjain
12)SMS College,Jaipur
13)Christian medical collage,Vellore, TN

**Function**

1)To optimize safe & effective Use of medicines In set up.
2.to create awareness amongst Healthcare professionals about the importance of ADR reporting.
3)To monitor benefit risk profile of medicines.
4)Generate independent evidence Based To commendations on the safety of medicines.
5.collection of ADR Reports.
6.perform follow up with the complainant To check completeness as per Sops.
7.Data entry into Virgiflow.
8.Reporting to PVPI Noc through Vergiflow with the source data allachnected to the ADR COGO
9) Training/feed back to physicians through Newsletters circulated by the PVPT NCC.
10.centre coordinator responsible for sending Monthly report to AMC

- *Azithromycin*
- *Azithromycin is a macrolide antibiotic used to treat a variety of bacterial infections.*
- *Azithromycin is an antibiotic medication used for the treatment of a number of bacterial infections.*
- *This includes middle ear infections, strep throat, pneumonia, traveler's diarrhea, and certain other intestinal infections.*
- *Along with other medications, it may also be used for malaria.*

- *Introduction :-*

- *It is primarily used for the treatment of respiratory, enteric and genitourinary infections and may be used instead of other macrolides.*
- *Azithromycin is an azalide, a type of macrolide antibiotic.*
- *It works by decreasing the production of protein, thereby stopping bacterial growth.*

- *DISCOVERY :-*
- *In the late 1970s, a team of Pliva's researchers discovered an antibiotic named Azithromycin.*
- *Azithromycin was discovered in 1980 by the Croatian pharmaceutical company Pliva and approved for medical use under the brand name Sumamed in 1988.*
- *It is on the World Health Organization's List of Essential Medicines.*
- *The World Health Organization classifies it as critically important for human medicine.*


- ➢ *STRUCTURE :--*
- ➢ *BRAND NAME :-*
- ➢ *Azasite,*
- ➢ *Zithromax,*
- ➢ *Zmax*
- ➢ *Azee*
- ➢ *Azicip*

,

- *route of administration:-*
  *Iv (intravenous route)*
  *Oral*
- *Dose :-*
  *250 mg (tablet)*
  *500mg (tablet*

- ➢ *WEIGHT :-*
- ➢ *Average: 748.9845*
- ➢ *Monoisotopic: 748.508525778*

- ➢ *FORMULATION OF MEDICINE :-*
- ➢ *TABLET,*
- ➢ *SYRUP,*
- ➢ *SUSPENSIONS,*
- ➢ *INJECTION,*

- ➢ *PHARMACOKINETIC :-*
- ➢ *ABSORPTION :-*
- ➢ *Although slightly less potent than erythromycin against gram-positive organisms, azithromycin demonstrates superior activity in vitro against a wide variety of gram-negative bacilli, including Haemophilus influenzae.*
- ➢ *Absorption is approximately 37% after a 500-mg oral dose.*
  *Bioavailability of azithromycin is 37% following oral administration. Absorption is not affected by food.*
- ➢ *Macrolide absorption in the intestines is believed to be mediated by P-glycoprotein (ABCB1) efflux transporters, which are known to be encoded by the ABCB1 gene 4.*

- ➢ *DISTRIBUTION :-*
- ➢ *Orally administration azitromycin is widely distributed over the whole body*
- ➢ *Pharmacokinetic studies have shown considerable higher azithromycin concentrations in the tissues, cup to 50 times the maximum concentration observed in the plasma than in the plasma.*
- ➢ *This indicate that the substance is extensively bound in the tissues (steady -state volume of distribution approximately 31, 1/kg)*
- ➢ *With the recommended dosage no accumulation in the serum/plasma occurs.*
- ➢ *Accumulation dose occurs in the tissue, where the levels are much higher than in the serum/plasma.*
- ➢ *Concentration in target tissue such as lungs, tonsil, and prostate exceed the MICgo for likely pathogens after single dose 500 mg.*
- ➢ *In experimental in vitro and in vivo studies, azithromycin accumulates in phagocytes realease is promoted by active phagocytosis.*
- ➢ *In animal models this process appeared to contribute to the accumulation of azithromycin in tissue.*

- The binding of azithromycin in tissue or plasma protein is variable and varies from 52% at 0.05 ug/ml to depending on the serum concentration

➢ METABOLISM :-
- In vitro and in vivo studies to assess the metabolism of azithromycin have not been performed . However, this drug is eliminated by the liver 8.
- The metabolism of Azithromycin can be increased when combined with Apalutamide.
- The risk or severity of adverse effects can be increased when Azithromycin is combined with Apixaban.

➢ ELIMINATION :-
- Biliary excretion of azithromycin, primarily as an unchanged drug, is a major route of elimination.
- Over a 1 week period, approximately 6% of the administered dose is found as unchanged in urine.
- Azithromycin is mainly eliminated unchanged in the feces via biliary excretion and trans intestinal secretion.
- Urinary excretion is a minor elimination route: about 6% and an oral dose and 12% of an intravenous dose are recovered unchanged in urine.

● Over dose:-

This may cause liver damage and irregular heart rhythm

.

● Adverse effects:-

Diarrhea.
Being sick (vomiting)
Losing your appetite.
Headaches.
Changes to your sense of taste.

● Drug drug interactions:-

Other drugs that may interact with azithromycin include:
digoxin, a heart medication.
colchicine, a gout medication.
phenytoin, a seizure medication.
antacids that contain magnesium or aluminum.

● Use :-

Azithromycin is used to treat certain bacterial infections, such as
bronchitis,
pneumonia,
infections of the ears,
lungs,
sinuses, skin, throat.

➢ HALF - LIFE :-
- Terminal elimination half-life: 68 hours.

➢ CLEARANCE :-
- Mean apparent plasma cl=630 mL/min (following single 500 mg oral and i.v. dose).

➢ PROTEIN BINDING :-
- The serum protein binding of azithromycin varies in humans, decreasing from 51% at 0.02 g/mL to 7% at 2 g/mL.

➢ PHARMACODYNAMIC :-

- *Macrolides stop bacterial growth by inhibiting protein synthesis and translation, treating bacterial infections 4.*
- *Azithromycin has additional immunomodulatory effects and has been used in chronic respiratory inflammatory diseases for this purpose 3.*
- *antimicrobial activity by binding to the 50S ribosome and inhibiting protein translation.*
- *H. influenzae mechanisms of resistance against macrolides include ribosomal methylase, intrinsic or acquired efflux pumps, and alterations in ribosomal proteins or RNA*

- *INDICATION :-*
- *Azithromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria in order to prevent the development of antimicrobial resistance and maintain the efficacy of azithromycin.*
- *Azithromycin is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the microorganisms listed in the specific conditions below.*
- *Recommended dosages, duration of therapy and considerations for various patient populations may vary among these infections.*
- *Refer to the FDA label and Indications section of this drug entry for detailed information*

- *ADULT :-*
- *Acute bacterial exacerbations of chronic obstructive pulmonary disease due to Haemophilus influenzae, Moraxella catarrhalis or Streptococcus pneumoniae.*
- *Community-acquired pneumonia due to Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae or Streptococcus pneumoniae in patients appropriate for oral therapy.*
- *Acute bacterial sinusitis due to Haemophilus influenzae, Moraxella catarrhalis or Streptococcus pneumoniae.*
- *Pharyngitis/tonsillitis caused by Streptococcus pyogenes as an alternative to first-line therapy in individuals who cannot use first-line therapy. Uncomplicated skin and skin structure infections due to Staphylococcus aureus, Streptococcus pyogenes, or Streptococcus agalactiae. Abscesses usually require surgical drainage.*
- *Urethritis and cervicitis due to Chlamydia trachomatis or Neisseria gonorrhoeae.*
- *Genital ulcer disease in men due to Haemophilus ducreyi (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.*

- *PEDIATRIC PATIENTS :-*
- *Acute otitis media caused by Haemophilus influenzae, Moraxella catarrhalis or Streptococcus pneumoniae*
- *Community-acquired pneumonia due to Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae or Streptococcus pneumoniae in patients appropriate for oral therapy.*
- *Pharyngitis or onsillitis caused by Streptococcus pyogenes as an alternative to first-line therapy in individuals who cannot use first-line therapy.*

- *MECANISM OF ACTION :-*
- *In medicine, a term used to describe how a drug or other substance produces an effect in the body.*
- *In order to replicate, bacteria require a specific process of protein synthesis, enabled by ribosomal proteins 6.*
- *Azithromycin binds to the 23S rRNA of the bacterial 50S ribosomal subunit. It stops bacterial protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit Label, 5.*
- *This results in the control of various bacterial infections 7, Label. The strong affinity of macrolides, including azithromycin, for bacterial ribosomes, is consistent with their broad-spectrum antibacterial activities 7.*
- *Azithromycin is highly stable at a low pH, giving it a longer serum half-life and increasing its concentrations in tissues compared to erythromycin 4.*

- *PRECLINICAL SAFETY DATA :-*

- ➢ *In animal study using exposures 40 times those achieved at the clinical therapeutic dosage , azithromycin was found to have caused reversible phospholipids, but as a rule there were no associated toxicological consequences.*
- ➢ *The relevance of this finding to human receiving , azithromycin in accordance with recommendation is unknown*
- ➢ *Electrophysiological investigation have shown that azithromycin prolongs the QT interval.*

- *CARCINOGENIC POTENTIAL :-*

*Long term studies in animal have not been performed to evaluate carcinogenic potential*

- *MUTAGENIC POTENTIAL :-*
- *There was no evidence of a potential for genetic and chromosome mutations in vivo and in vitro test models.*

- *REPRODUCTIVE TOXICITY :-*
- *No teratogenic effects were observed in embryonic toxicity studies in rats after oral administration of azithromycin.*
- *In rats, azithromycin dosage of 100 and 200 mg/kg, body weight/ per day led to mild retardation in fetal ossification and maternal weight gain.*
- *In peri and postnatal studies in rat mild retardation following treatment with 50 mg/ kg / day. Azithromycin and above were observed.*

- ➢ *CLINICAL TRIALS :-*
- ➢ *The clinical trials are conducted by giving azithromycin shown in the following survey.*
- ➢ *Aim :-*

*The safety and scientific validity of this study is the responsibility of the study sponsor and investigator.*

- *The risk and potential benefits of clinical studies and talk to your health care provider before participating.*
- ➢ *Therapeutic indicator :-*

*Azithromycin film coated tablets are indicated for the following bacterial infection induced by microorganisms susceptible to azithromycin.*

- ➢ *Infection of the upper respiratory tract :-*

*acute bronchitis and mild and mild to moderate community acquired pneumonia.*

- ➢ *Infection of the skin and soft tissue of mild to moderate severity. severity*

*Eg :- cellulite, folliculitis.*

- ➢ *METHOD OF ADMINISTRATION :-*

*Azithromycin film coated tablet should be taken in a single daily dose*
*The tablet should be swallowed whole and may be taken with or without food.*
*The length of treatment for various infections and diseases.*

1. *Children and adolescents with a baby weight above 45 kg adult and the elderly :-*

*The total dosage of azithromycin is 1500 mg, staggered over three days (500 mg once daily). Alternatively the dosage may be staggered over five days (500 mg as a single dose on the first day and then 250 mg once daily).*

2. *Elderly patients :-*

*The same dosage as in adult patients is used in the eldrly patient can be patient with on going proarrhythmia andtorsades de pointes.*

- ➢ *SELECTION OF DRUG :-*

*Selection of drug class for pharmacovigilance study using different criteria.*
*(eg. Commercial availability, selling of drugs etc.)*

- ➢ *Availability :-*

*Azithromycin is available in many forms.*

- *Tablet,*
- *Syrup,*
- *Suspension,*
- *Injection*

- *It is an antibiotic available over the counter without a prescription.*
- *Azithromycin is a prescription drug which means a doctor needs to prescribe it for you.*
- *OTC medications don't required a prescription*
- *Azithromycin market size research report identifies new revenue opportunity in availability of azithromycin tablets as generic and brand names drugs.*

➢ *SELLING OF DRUG :-*

➢ *The global azithromycin market size was significantly robust in 2020 and is expected to register a double digits revenue AGR over the forecast period.*

➢ *Major factors driving market revenue growth are increasing prevalence of bacterial infections, rising focus on expanding application scope of azithromycin for different indications and increasing availability of azithromycin tablets as generic and brand name drugs.*

➢ *In addition, rising investment and funding to accelerate research activities in the pharmaceutical sector and increasing number of product approvals from regulatory authorities contributed to market growth going ahead.*

➢ *Azithromycin was also studied as a part of possible treatment approach for covid- 19.*

➢ *Azithromycin is also used in children for treatment of ear and chest infection.*

➢ *Wild usage of azithromycin to treat various diseases is expected to further boost demand for the drug and contribute to revenue growth of the market over the forecast period.*

➢ *Products out look :-*

➢ *Based on product, the global market has been segmented into oral, injection, and topical ophthalmic. Oral segment is expected to account for the largest revenue share in the global market owing to increasing preference for oral administration of azithromycin as it is readily absorbed on empty stomachs.*

➢ *Azithromycin is actively transported to site of infection due to its high concentration in phagocytes.*

➢ *Administration of a single oral dose of azithromycin can maintain the required bacteriostatic level in infected tissues for several days, and this is a key factor contributing to revenue growth of this segment.*

➢ *Azithromycin is actively transported to the site of infection due to its high concentration in phagocytes.*

➢ *Administration of single oral dose of azithromycin can maintain required bacteriostatic level in infected tissues for several days, and this is a key factor contributing to revenue growth of this segment.*

➢ *Companies Profiled in the Report :-*

➢ *Some major companies in the market include Pfizer, Inc., Akorn Inc., Teva Pharmaceuticals Industries Ltd., Mylan, Zydus Pharmaceuticals, Sandoz, Pliva, Wockhardt Ltd.*

➢ *Lupin Limited, Gland Pharma Limited, Aurobindo Pharma, Hainan Hailing Chemipharma Corporation Ltd., and CSPC Pharmaceutical Group Limited.*

➢ *Major companies are undertaking strategic initiatives such as mergers and acquisitions, joint ventures, collaborations, R&D activities, and product developments to gain a robust footing in the market.*

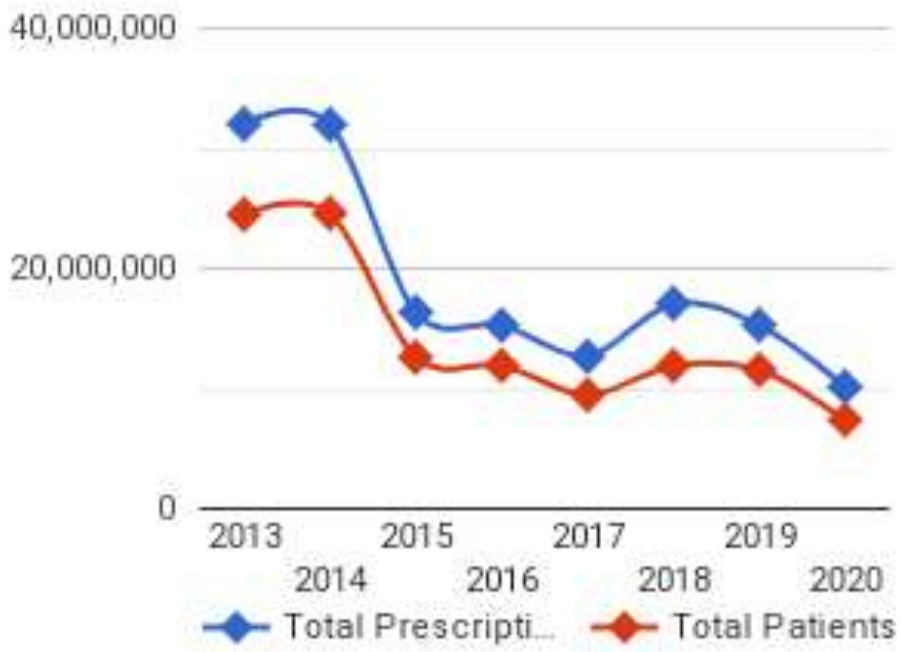
- *Azithromycin summary :-*

| | |
|---|---|
| *TOp drug rank* | *# 68 ( decrease in 2020)* |
| *Estimate number of prescription in the United State ( 2020)* | *10,155,807* |
| *Estimate number of patient in the United State* | *7,405,927* |

- *Average out pocket cost (USD)*

| | |
|---|---|
| *Per prescription* | *$28.38* |
| *Per day of therapy* | *$3.68/day* |

- *Total Prescriptions and Patients Per Year (2013 - 2020)*




- *RANK OF TOP DRUG OVER TIME :-*
- *Rank refers to the frequency that a given medication is prescribed within a calendar year compared to all other medications. A rank of "4" would indicate that the medication was the fourth most commonly prescribed medication.*
-

| YEAR | RANK | CHANGE |
|---|---|---|
| 2013 | 17 | ↓ 1 |
| 2014 | 16 | ↑ 1 |
| 2015 | 52 | ↓ 36 |
| 2016 | 48 | ↑ 4 |

-

| YEAR | RANK | CHANGE |
|---|---|---|
| 2017 | 56 | ↓ 8 |
| 2018 | 45 | ↑ 11 |
| 2019 | 48 | ↓ 3 |
| 2020 | 68 | ↓ 20 |

- *Drug cost over time (2013- 2020)*
- *COST PER PRESCRIPTION FILL :-*

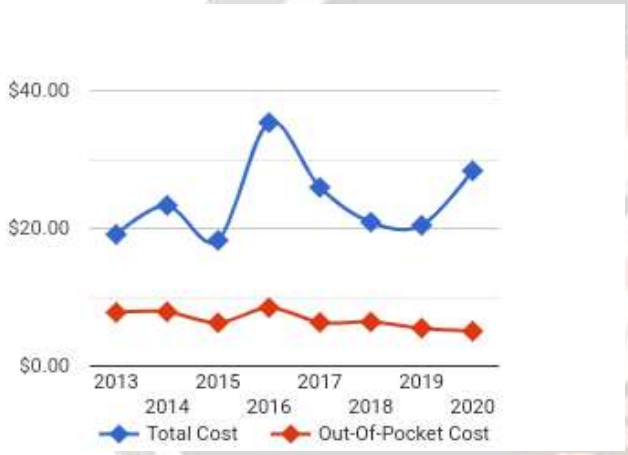
*Average cost per filled prescription regardless of how many days of therapy the prescription is filled for.*
*Eg. 10 days, 30 days, 90 days.*

- *COST PER DAY OF THERAPY :-*
  *The average cost per prescription fill divided by the days of therapy, for example a 10 days antibiotic course costing $30 would be $3 per day. Similarly, a 30-day supply of an oral antihypetensive costing $30 would be $1 per day.*

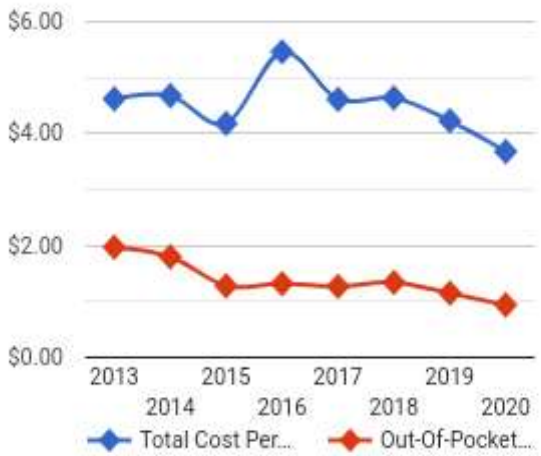
- *Total cost :-*
  *average total cost of the medication including the out-of-pocket cost (see below) plus the amount paid by other parties (Medicare, Medicaid, private insurance, Veterans Administration, TRICARE, other state/federal sources, Worker's compensation, and other miscellaneous sources).*

- *Out of poket cost :-*
  *The average payment made by the patient which may include deductibles, coinsurance, copayments, or the cash price paid without insurance coverage.*

- *Cost per prescription fill (USD) :-*




- *Cost per Day of therapy :-*

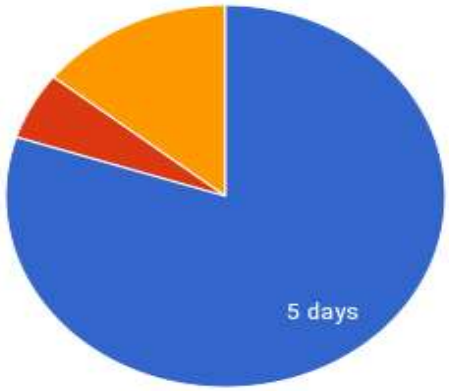



- *Distribution of Dispensed Dosage forms (2020) :-*

| *Dosage form* | *Strength* | *% of Dispensed products* |
|---|---|---|

| | | |
|---|---|---|
| *Tablet/ capsule* | *250 mg* | *80.7%* |
| *Tablet / capsule* | *500 mg* | *12.9%* |
| *Other, unspecified, or misc.* | *-* | *6.4%* |

- *Disribution of Days supplied (2020) :-*
  *Days supply" is defined as the number of days that a prescription should last. For example, a prescription of 60 tablets that is taken twice daily has a day supply of 30 days.*




- *RELETED DRUGS :-*

| *DRUG NAME* | *TOTAL PRESCRIPTION (2020)* |
|---|---|
| *Azithromycin drug* | *10, 155,807* |
| *Erythromycin* | *2,09,153* |
| *Clarithromycin* | *274,951* |

- *Therapeutic classes :-*
- *Anti - infective,*
- *Macrolide Derivatives,*
- *Macrolide.*
-
- *Drug synonyms :-*
- *Drug synonyms are used during the sanitation and standardization process of cleaning the original data source ( MEPS).*

- *Occasionally brand names may be listed below that are no longer on the market or are very infrequently used.*
- *Brand name synonyms :-*
  *Azasite,*
  *Zithromax,*
  *Zmax,*
  *Azithromycin.*

- *Generic Drug synonyms and salts : -*

*Azithromycin anhydrous,*
*Azithromycin Dehydrate,*
*Azithromycin monohydrate,*
*Azithromycin unspecified form,*
*Azithromycin*
*FDA APPROVAL INFORMATION :-*

| | |
|---|---|
| *Established pharmacological class (EPC)* | *Macrolide, antimicrobial* |
| *Initial FDA Approved date* | *11/01/1991* |
| *First FDA Applicant* | *Discn* |
| *First dosage form* | *Capsule (oral)* |

WHAT ARE SIDE EFFECTS ASSOCIATED WITH USING AZITHROMYCIN?

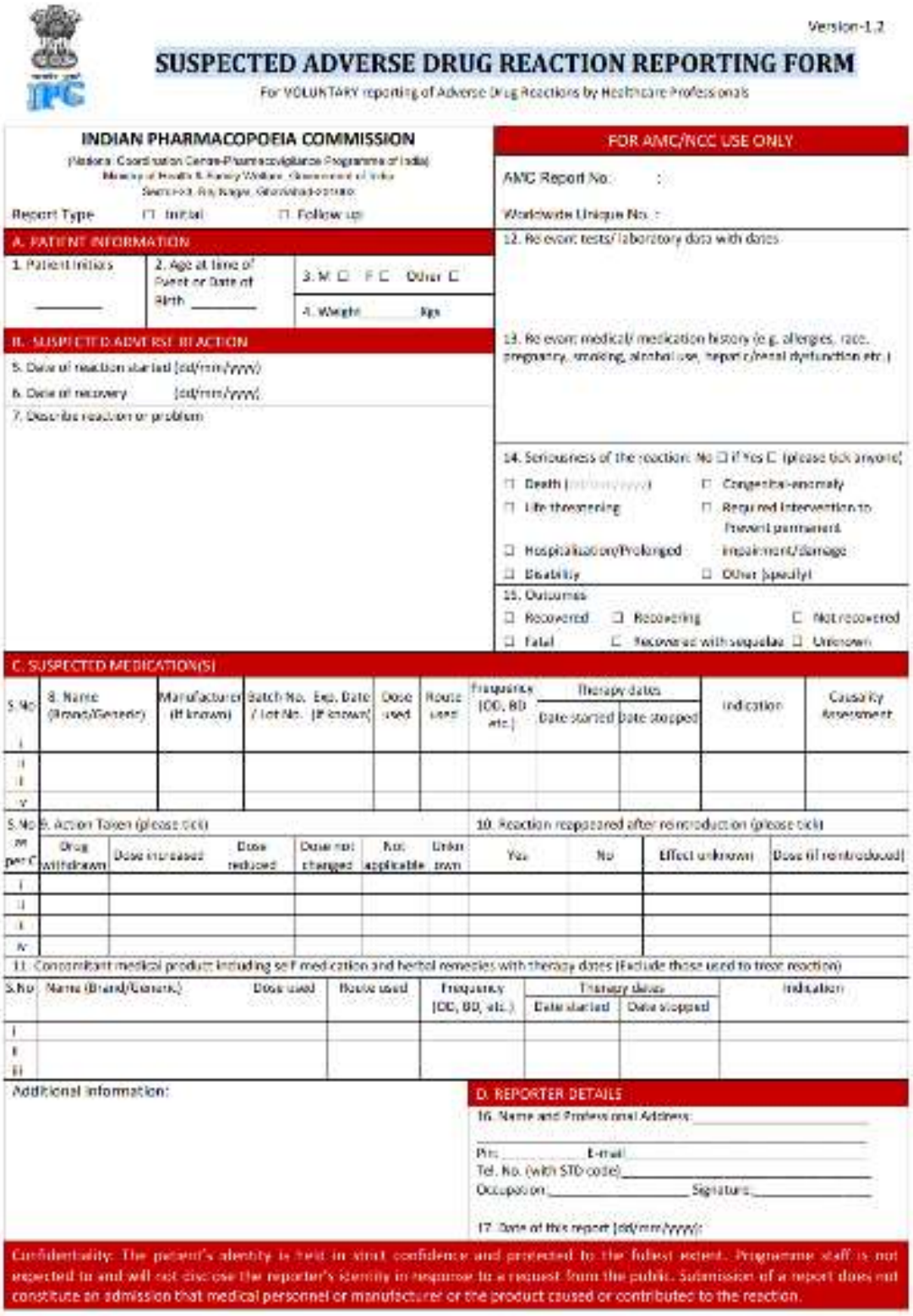
Side effects of azithromycin include:

- Diarrhea
- Nausea
- Abdominal pain
- Loose stool
- Cramping
- Vaginitis
- Indigestion
- Gas
- Vomiting
- Feeling unwell (malaise)
- Agitation
- Allergic reaction
- Anemia
- Loss of appetite
- Yeast infection (candidiasis)
- Chest pain
- Pink eye (conjunctivitis)
- Constipation
- Dermatitis (fungal)
- Dizziness
- Eczema
- Swelling
- Intestinal inflammation
- Fatigue
- Stomach upset
- Headache
- Hyperkinesia

- Low blood pressure (hypotension)
- Increased cough
- Insomnia
- Low white blood cell count (leukopenia)
- Black, tarry stool
- Mucositis
- Nervousness
- Oral thrush
- Pain
- Palpitations
- Sore throat
- Fluid around the lungs
- Itching
- Pseudomembranous colitis
- Rash
- Runny nose
- Seizures
- Somnolence
- Hives
- Spinning sensation
- Vertigo

Additional side effects of azithromycin from post marketing reports include:

- Severe allergic reaction (anaphylaxis)
- Skin swelling
- Bronchospasm
- Constipation
- Skin reactions
- Elevated liver enzymes
- Skin redness
- Pancreatitis
- Pyloric stenosis, rare reports of tongue discoloration
- Stevens-Johnson syndrome
- Torsades de pointes
- Toxic epidermal necrolysis
- Low white blood cell count (neutropenia)
- Elevated bilirubin, AST, ALT, BUN, creatinine
- Alterations in potassium
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)



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

Report Type: ☐ Initial ☐ Follow up

**FOR AMC/NCC USE ONLY**

AMC Report No. :

Worldwide Unique No. :

**A. PATIENT INFORMATION**

1. Patient Initials _____

2. Age at time of Patient or Date of Birth _____

3. M ☐ F ☐ Other ☐

4. Weight _____ Kgs

**B. SUSPECTED ADVERSE REACTION**

5. Date of reaction started (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

12. Re event tests/laboratory data with dates

13. Re event medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)

14. Seriousness of the reaction: No ☐ If Yes ☐ (please tick anyone)

☐ Death (dd/mm/yyyy) ☐ Congenital anomaly

☐ Life threatening ☐ Required intervention to Prevent permanent

☐ Hospitalization/Prolonged impairment/damage

☐ Disability ☐ Other (specify)

15. Outcomes

☐ Recovered ☐ Recovering ☐ Not recovered

☐ Fatal ☐ Recovered with sequelae ☐ Unknown

**C. SUSPECTED MEDICATION(S)**

| S.No | 8. Name (Brand/Generic) | Manufacturer (If known) | Batch No. Exp. Date / Lot No. (If known) | Dose used | Route used | Frequency (OD, BD etc.) | Therapy dates: Date started | Therapy dates: Date stopped | Indication | Causality Assessment |
|---|---|---|---|---|---|---|---|---|---|---|
| i | | | | | | | | | | |
| ii | | | | | | | | | | |
| iv | | | | | | | | | | |

| S.No (as per C) | 9. Action Taken (please tick): Drug withdrawn | Dose increased | Dose reduced | Dose not changed | Not applicable | Unknown | 10. Reaction reappeared after re-introduction (please tick): Yes | No | Effect unknown | Dose (if re-introduced) |
|---|---|---|---|---|---|---|---|---|---|---|
| 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: Date started | Therapy dates: Date stopped | Indication |
|---|---|---|---|---|---|---|---|
| i | | | | | | | |
| ii | | | | | | | |
| iii | | | | | | | |

Additional information:

**D. REPORTER DETAILS**

16. Name and Professional Address: _____

Ph: _____ 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 contributes to the reaction.

- Reference:-

https://www.dovepress.com/in-vitro-activity-and-pharmacodynamicpharmacokinetic-parameters-of-cla-peer-reviewed-fulltext-article-IDR

https://www.mayoclinic.org/drugs-supplements/azithromycin-oral-route/side-effects/drg-20072362?p=1

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https://www.drugs.com/ingredient/azithromycin.html

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https://go.drugbank.com/drugs/DB00207