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Study of pharmacovigilance related drug Caffeine

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Abstract:

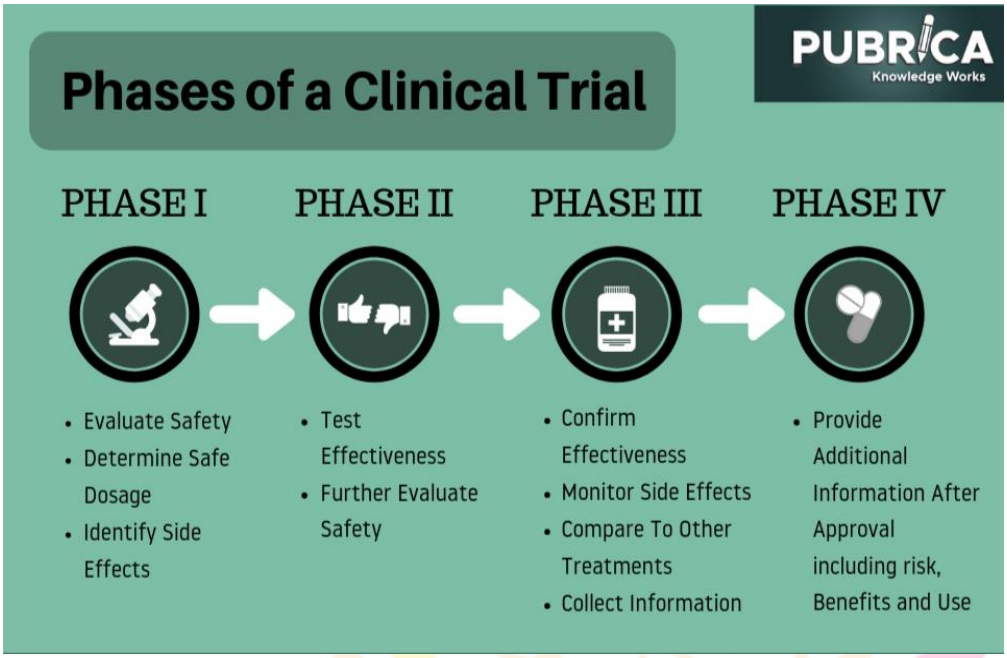
Pharmacovigilance (PV or PhV), also known as Drug Safety, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. Caffeine, a component of coffee, soft drinks, and chocolate, is widely consumed and considered harmless, although it has powerful effects on a number of organs, systems, and behavior. Caffeine, in typical concentration ranges of human consumption, acts as a nonspecific blocker of the adenosine receptor.

Caffeine is the most widely consumed behaviorally active substance in the world. The behavioral effects of caffeine have been reviewed many times (e.g., Lieberman, 1992; Fredholm et al., 1999; Smith, 2002) and this chapter overviews the main findings and provides an update of recent research. Caffeine produces its behavioral effects through adenosine receptor antagonism and subsequent changes in many neurotransmitter systems. This result in increased alertness and caffeine may be especially beneficial in low arousal situations (e.g., working at night, prolonged work, or sleep deprivation). It improves performance on tasks that are impaired when alertness is low (vigilance and sustained response). Such effects largely reflect increased turnover of central noradrenaline. Although it has strong impacts on a number of organs, systems, and behaviours, caffeine, an ingredient in coffee, soft drinks, and chocolate, is frequently ingested and perceived as innocuous. When consumed in typical human concentration ranges, caffeine serves as an all-purpose adenosine receptor blocker.

Keywords: Pharmacovigilance, toxicology, cervical cancer, human papillomavirus, Caffeine

Introduction:

Clinical trials are scientific research and investigation in which. people to test new treatment interventions or test as meant to prevent, detect, treat or manage various diseases or medical conditions.



- People volunteer to take a part of clinical trials to test a medical intervention including drugs,cells,& others biological product, surgical procedure and other radiological process,devices, behavioural treatment &preventive care.
- Clinical trials are carefully designed, reviewed and complete and need to be approve before they can start.
- People of all ages can take part in clinical trials, including children.
- It is a systematic investigation in human subjects for evaluating the safety and efficacy of any drug.
- It is are a set of test in medical research and drug development that generates safety and efficacy data for health intervention in human being.
- There are the mainly two types in clinical research.
- Preclinical trial.
- Clinical trial

Preclinical Trials:-
Toxicokinetic and Pharmacokinetic studies:

- In Vitro metabolite data animal and human and dato, in animal should be evaluated initiating human clinical trials.

- further absorption, distribution metabolism, animal and excretion should be available for treating long duration
- **Acute Toxicity studies.**
- Acute toxicity information has been obtained from single dose toxicity studies in two species using both clinical and parenteral route of administration.
- This is available to phase-III clinical trials for higher risk for overdose. (Eg) depression,pain.

- **Repeated dose Toxicity studies:**
- In principle the duration of Animal toxicity studies in two mammalian species Cone - non-rodent) should equal, to exceed the duration of human clinical trials up to maximum education of repeated toxicity studies.

- **Local tolerance studies:**

  To evaluate local tolerance by intended therapeutic route as part of general toxicity studies.

- To Support a limited administration by non- therapeutic range. eg- (Single - IV]

- **Nontoxicity studies**

- An assay for gene mutation generally considered Sufficient to Support all Single clinical development trials.

- **Carcinogenecity_studies**.
- It should be conducted for Marketing Application.
- For pharmaceutical develop. Certain Serious disease for adult pediatric patients - Carcinogenicity testing.
- **Reproduction Toxicity**
- It should be Conducted appropriate population for exposure.
- there are following four Categories men, women, not child bearing, women not child bearing in pregnant women.
- Other Toxicity

Non- Clinical Study

- eg) Identify potential biomarkers.

Clinical Phase Trial:

According to ICH guidelines clinical trials should be Conducted and Analyzed according to Sound Scientific principle, with. regard to ethical Consideration in order to achieve the trials objectives.

>Types of clinical Trials

- **Phase 0**
- **Phase I**
- **Phase II**
- **Phase III**
- **Phase IV**

Phase: - 0

- **Participants: - 10-20**
- **Trial length :- Less than one week**
- Medication acts differently than expected, the investigators will likely to Some additional preclinical research before deciding whether to continue the trial.
- Example - Due to unknown risk posed. The sample volunteers selected by this phase are very small, usually 10-12 individuals.

- The people chosen are usually healthy Volunteers. Due to unknown risk Surrounds use Small amount drugs for seven days to minimize it ADE.
- The aim of phase i trials is not to test its therapeutic effect but to check that the drug behaves as expected in humans & gather preliminary data regarding what the drug does to the body and what the body does to the drug.

Phase-I [Human Pharmacology]:-

- **Participants: - 20-80**
- **Trial length: - Month to One Year.**
- During phase I of clinical trials investigators Spend several months looking at the effect of the medication on about 20 to 80 people who have no health Condition .
- The phase aims to figure out the highest dose humans can take without Serious Sideeffects.
- In clinical trial phase the Collected information are
- The Most Common side effect.
- How your body responds to Treatment.
- What dose of the Treatment works the best?
- > Selection of Dose
- Safety & tolerability
- maximum tolerated dose

Phase II:-

- **Participants :- 100-300**
- **Trial length :- Several Month to Two years.**
- Therapeutic exploratory trials
- first trials in patients - to be treated. with disease
- to evaluate in particular indicators.
- patients test :- effectiveness
- Place :- Specialized hospital units.
- I) Phase I I A :- open uncontrolled trial small of patient Determine dose ranges.
- Phase II B:- Placebo controlled, Double blind determined clinical dosage schedule established of beneficial and undesirable effect.

- **Phase-III Trials:-**

- **i) Confirmatory**
- **ii) multi-centric trials**
- **Participants :- 300- 3000**
- **Trial length :- 1 to 4 years.**
- IIIA] Trials carried out on large no or Special Category
- e:g) patient with renal failure.
- IIIb] Extended trials of III A after apply for approval but Before lunch
- > Randomized clinical Trials
- A) placebo Control :- Compare one or more ingredient treatment to dosage form not containing active treatment.

  e:g) Ibuprofen and Lactose

- [B] Active Treatment Compare two or more treatments each with diff. ingredients
- e. g) Ibuprofen & Diclofenac
- Dose - Comparison concurrent Control Compare diff dose regimen of Same treatmentE:g) 200mg od 400 mg of Ibuprofen for paining.

PHASE IV:-

- studies required as a condition of approved by FDA
- i) Additional efficacy | Safety profile. ii) New Indication
- become phase - APR study.
- >Categories of phase IV clinical trial
- i) pharmacovigilance, post market Surveillance study (PMS)
- ii) Comparative study.
- Studies for new indications, dosage & Formulation. .
- IV Market oriented including seeding trials.
- post marketing Surveillance
- ADE detected by phase IV trials may result in withdrawal of the drug.

- A] Thalidomide - used in the morning as Sickness but withdrawn as a result ofphocomelia.
- Troglitozone use as antidiabetic drug but caused drug induced hepatitis.
- > Pms is phase IV study.
- >post marketing study design
- Cross-sectional studies
- e:g) Survey or prevalence studies
- B) Case Controlled studies
- eg) To investigate whether there is an association between drugs. .
- C) Cohort studies
- e-g) to know the incidence rate.
- > Ethical issue is phase IV marketing studies, Safety efficacy, comparative efficacy etc

An approach to classifying clinical studies according to objective..

Type of study	Objective	Study of example
1) Pharmacology	Asses tolerability describedpk and pd exploring drug metabolism and drug interaction	Dose tolerability single and multiple dose pk and pd and drug interaction
2) Therapeuticexploratory	• Explore use for the target indications • Estimated dosage for subsequent study • Provide basis for end point methodology	• Earliest trial of relatively shortduration • Dose response exploration studies
3) Therapeutic use	• Understanding of benefits risk relationship in general or special populations • Identify less common adr	• Study of mortality morbidity • Large sample trial • Pharmacoeconomic study

Drugs and Clinical Trial Rules 2019

- ICH:-international conference of harmonization
- Ich :- Good clinical practice
- Quality data+ethics - GCP (good clinical practice)

The Good clinical practice cover the step including:-

- Design
- Performance
- Monitoring
- Auditing
- Analysis
- Reporting

Objective:-

- To provide an overview of history of good clinical practice (international conference harmonization)
- Too emphasis importance of the ich gcp compliance when conducting clinical trial
- To the recognise implications of the non compliance
- To review positive and negative cause studies
- To protect the patient

Scope of GCP:-

- Good clinical laboratory should be the used by the all laboratory where the test are the done on biological specimen diagnosis patient care disease contro

- Microbiological and serology
- Hematology and blood banking
- Molecular biology and molecular pathology
- Clinical pathology
- Histopathology

Key changes in 2019 New drug and clinical trial Rule:-

- In new rule 2019 such as. The research has been defined to include studies on the basic applied and operational research or clinical research design primarily to increase scientific knowledge about disease and the condition behavior their detection and cause and evolving strategies health promotion prevention does not disease rehabilitation doesnot disease include.
- In vitro diagnosis (IVDS) performance testing for research
- New surgical intervention
- Assisted reproductive technology
- Public health survey
- Epidemiology health survey
- Observational and non-interventional study of old drug
- These type study should be approved ethics committee constituted under the 16 registerunder rule 17 with CDSCO office as ethics committee for biomedical and health research

Academic clinical trial:-

- New rule 2019 described academic Clinical trial as clinical trials of drug already approved for certain drug already claim and initiated by investigator .academic research institutions for the new indications or new route of administration or the new dose or new dosage form
- Some important points for academic clinical trial including:-
- Only for approved drug
- CT initiated investigators academic or research authority,new route new response inindications or new dosage form
- Ec can seek clarity from the central license authority and the CLA respond in 30 days or the deemed that no approval needed medical management and compensation applicable as per ICMR guidelines.biomedical research on the human participate academic required conduct accordance with CTProtocol approval EC and ethical principles specified in the ICMR guidelines for biomedical research human participants

Ethics committee (ECS):-

- As delineated in the 2019 CT rule and additional resources.india has the decentralized process for the ethical review or the clinical trial application and required ethical committee EC approval for each trial use.
- In accordance with 2019 CT rule and additional resources A all ethics committee ECS that'review drug clinical trials are required to the registered with new drug controller general of India DCGT head of drug general standards control organization and approving clinical trial protocol.
- In addition to the 2019 CT rule established a separate registration and monitoring system for ECS that overase biomedical and health research studies
- Per notice 15 sep 19 and chapter 4 of the 2019 CT rule any institute organization that plans to conduct biomedical and health research involving Human participation is now required to have EC to review and oversee conduct such research before study.

EC Composition:-

- Pursuant to the 2019 CT rule and ICMR guidelines institutions independent EC should be the multidisciplinary multi-sectoral representing mixed gender age composition
- As per 2019 CT rule ICMR guidelines composition should include following-
- Chairperson from outside the institute
- One (1) to two (2) basic medical scientist (preferably one (1) pharmacologist)
- One (1) to two (2) clinical from various institutions
- Legal experts or retried judge
- One (1) social scientist/representative/non government voluntary agency
- One (1) philosopher / ethicist
- One(1) lay person from community
- Member secretary alternative member secretary optional
- One (1) member independent institutions is non scientific

Advised to check with CDSCO if truly old drug:

- There is an expectation that the number of phase 4 studies being conducted in India will increase. This expectation is based on the assumption that with local clinical trials waiver a phase 4 study might need to be conducted except in special situations.

Orphan drug registration

- 2019 rules defined orphan drug as a drug intended to treat a condition which defects not more than five lakh people in India.
- Provision for fast track approval process and special status for orphan drugs including a complete fee waiver for CT feeling.
- Provision for expeditious review process.
- Provision for waiver of local clinical study of phase 4 on satisfaction of CLA.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and preventionof adverse effects or any other medicine / vaccine rated problem for patient's safety.

Objective:-

- Improvement of patients care and safety in relation to the use of medicine and paramedical intervention remains to be an important parameter.
- The main objective of pharmacovigilance involves exhibiting the efficacy of drug by monitoring their adverse effects profile for many years from the lab to the pharmacy ; tracking and drastic effect of drug improving public health and safety in relation to the use of medicine.
- Promoting understanding education and clinical training in pharmacovigilance and effective communication to the general public.
- In addition, providing information to consumer practitioners and regulators on the effective use drug .

Caffeine

- Elements of the non-clinical and clinical safety specification
- Identification and evaluation of risks including drug-drug interactions anddrug-food
- Interactions

- Design and conduct of observational studies

Introduction

- Caffeine is naturally occurring stimulants that are found in coffee,tea,and other drinks and foods.
- Caffeine functions by stimulating the brain and central nervous system (CNS)
- Prevents the onset of tiredness
- It Takes about 1 hour to take effect and lasts for 3-4 hours.
- Caffeine utilizes the receptors on cells that adenosine bind to as a result the cell cannot recognize adenosine any more
- Consequently the adenosine cannot slow things down and instead everything speedsup.
- This can cause alertness since nerve cells activity ramps up.

Caffeine has bath short term and long term effects on the body

- Central nervous system.
- Headaches, migraines, confusion, anxiety , irritability.
- Digestive and excretory system heartburn ,upset stomach increased urination
- Circulatory and respiratory system increased blood pressure irregular heart rhythms
- Skeletal and muscular system osteoporosis achy muscles

Structure:

Structure of Caffeine

Mechanism of action

Caffeine action is thought to be mediated via several mechanisms.

The antagonism of adenosine receptors, the inhibition of phosphodiesterase, the release of calcium from intracellular stores and antagonism of benzodiazepine receptors.

Adverse effect of caffeine

Most of the people it is not harmful to consume up to 400mg of caffeine a day ,if eat or drink too much caffeine, it can cause health problems such as restlessness and shakiness.

Toxicity

The clinical features of caffeine intoxication army but have been reported to include cardiovascular symptoms (hypertension, hypotension, tachycardia, bradycardia,atrioventricular block supro ventricular, tachycardia ischemia ,myocardial infarction and cardiac arrest) gastrointestinal symptoms (nausea vomiting servers recurrent vomiting abdominal pain diarrhea) psychological neurological symptoms musculoskeletal symptoms (weakness rigidity tremor rhabdomyolysis) pulmonary symptoms (hyperventilation respiratory failure tinnitus dizziness , diuresis and death.

Discovery and development

Friedlieb range who is celebrated today was the discovery of caffeine and the frist person to isolate quinine bul his contribution of chemistry is often overlooked .he also invented paper chromatography a method for separating chemicals which is widely used in teaching labs . Range was born in Germany in 1794 the son of a poster the third of seven children Genotoxicity

One area which has received a great deal of attention is the potential genotoxic property of caffeine to better understand whether caffeine itself or in combination with other agent exhibit genotoxic effects. Hundreds of research studies published over the past 5 years have been reviewed.

Efficiency of caffeine

The doses of caffeine most likely to be effective without causing undesirable mood effects are within the range of 100 to 600 mg.

Reproductive toxicology

Caffeine is the most popular pharmacologically active substance consumed in the world .It is a stimulant that is often used to enhance mental alertness.

Although there is no high quality evidence that a modest level of caffeine consumption has adverse effect on fertility or pregnancy, outcome putative beliefs about a relationship between caffeine intake and adverse reproductive outcomes are common and caffeine consumption is often perceived to be can unhealthy habit. The consumption of caffeinated beverages has been implicated in fertility problems consumption during pregnancy has been associated with an increased risk of miscarriage ,congenital malformations ,stillbirth and long term behavioral effects in offspring.

Global market overview

The Caffeine Market size is estimated to reach $23.3 billion by 2027 and it is poised to grow at a CAGR of 7.2% over the forecast period of 2022-2027. Caffeine's expanding uses in numerous end-use industries, such as cosmetics and food and beverages, are likely to boost caffeine industry demand. And increased caffeine consumption to treat diseases such as colon, liver and colorectal cancers is fueling the caffeine market size. Caffeine is a white crystalline powder that is extracted from plants. It is known as a drug that stimulates the nervous system in the pharmaceutical industry. Caffeine levels in cocoa beans range from 0.1 to 0.7 percent. Caffeine can also be found in small levels in the skin that surrounds cocoa beans. Caffeine derivatives made from synthetic sources are known as synthesized caffeine. Unlike natural caffeine, which is derived from coffee, tea, cocoa leaves and other natural sources, synthetic caffeine is createdin a laboratory using a variety of chemical components. Urea and cyanoacetic acid are the major synthetic substances that are utilized to make synthetic caffeine.

Caffeine market report coverage

The "Caffeine Market Forecast (2022-2027)" by IndustryARC, covers an in-depth analysis of the following segments in the Caffeine Market.

By Type - Natural Caffeine and Synthesized Caffeine.

By End-user - Food & Beverages, Pharmaceuticals, Flavors & Fragrances, Skin Care Products and Others.

by Distribution Channel - Supermarkets/Hypermarkets, Convenience Stores, Discount Stores, Specialty Stores, E-commerce, and Others.

By Geography - North America (the U.S., Canada and Mexico), Europe (Germany, United Kingdom (UK), France, Italy, Spain, Russia and the Rest of Europe), Asia Pacific (China, JapanIndia, South Korea, Australia & New Zealand and Rest of Asia Pacific), South America (Brazil, Argentina, Chile, Colombia and Rest of South America) and Rest of the World (the Middle Eastand Africa).

Individuals' increasing intake of caffeinated beverages is a crucial driver driving the global caffeine industry forward.

Furthermore, rising health awareness and increased participation in sports and physical activities are driving global market size.

Caffeine's expanding uses in numerous end-use industries, such as cosmetics and food and beverages, are likely to boost caffeine industry demand.

Pharmacological effects of caffeine

The pharmacological effects of caffeine are similar to those of other methylxanthinesincluding those found in various teas and chocolates .

These effects include mild CNS stimulation and wakefulness, ability to sustain ,intellectual activity and decreased reaction time .

Caffeine can causes insomnia, nervousness ,restlessness ,nausea , increased heart rate and other side effects. Larger doses might cause headache anxiety and chest pain.

Caffeine is likely unsafe when used in very high doses

Drug interaction

Speeding up the nervous system stimulant medications can increase blood pressure and speed up the heartbeat.

Caffeine can also speed up the nervous system . Taking caffeine along with stimulantdrugs might cause serious problems including increased heart rate and high blood pressure

Contraindications of caffeine

- Severe anxiety
- Cardiovascular disease
- Peptic ulcer disease
- Hepatic impairment

- Renal impairment
- Seizures
- Pregnancy

Consumption report of selected drug

Consumption report of caffeine drug

Caffeine is naturally found in the fruit, leaves, and beans of coffee, cacao, and guarana plants. It is also added to beverages and supplements. There is a risk of drinking excess amounts of caffeinated beverages like soda and energy drinks because they are taken chilled and are easy to digest quickly in large quantities.

Overall caffeine consumption

Caffeine intake per day was measured in milligrams. A table was included in the questionnaire(Table 1). The common caffeinated drinks had been enlisted in the table. All common caffeinated drinks were investigated, including drinks such as coffee, decaffeinated coffee, tea, cola, citrus, and energy drinks.The table included the size and the number of cup/cans per dayfor each drink. A reference image was attached to illustrate the size, and the amount of fluid in ounces.

4oz	8oz S	12oz M	16oz L	20oz XL

Beverage category/ type/ description	Size of cup				Number of cups/cans per day
Caffeinated coffee					
Regular, brewed	S	M	L	XL	
K cups	S	M	L	XL	
instant	S	M	L	XL	
Prepared from flavored mix (e.g., pistachio latte)	S	M	L	XL	
Specialty coffees, with additional ingredients (e.g., latte, mocha, cappuccino, Americano)	S	M	L	XL	
espresso	S	M	L	XL	
Ready-to-drink, bottled or canned	S	M	L	XL	
Arabic coffee	Single size				
Decaffeinated coffee					
All types including regular, brewed, specialty, brand or brand not specified, ready-to-drink, bottled or canned	S	M	L	XL	
Tea					
Black tea	S	M	L	XL	
Green tea	S	M	L	XL	
Ready-to-drink, bottled tea	S	M	L	XL	
Carbonated soft drinks					
Cola: All types, caffeinated, regular or diet, including with added flavors (e.g., cherry cola), brand not specified	Single size				
Citrus: All types, caffeinated, brand specified	Single size				
Energy drinks					
bottles or cans, diet or regular	Single size				

Table No -01. Beverages intake by type, size, and number of cups.

The participants were asked to fill out only the size and number of the drinks they regularly consume. The Amount of caffeine in each drink size was calculated (Table 2), which were later multiplied by the number of cups/cans consumed daily. Then, the total numbers of caffeine milligrams per day were summed. Caffeine intake was examined as “low” and “high.” Low intake was considered less than 250 mg per day, while high intake was considered more than 250 mg per day. The validity and reliability of measurements have been confirmed in similar studies.Adverse effect of caffeine drugCaffeine

- ★ Insomnia
- ★ Restlessness
- ★ Nervousness
- ★ Tremor
- ★ Tinnitus
- ★ Irritability

- ★ Nausea
- ★ Vomiting
- ★ Diarrhea
- ★ Tachycardia
- ★ Diuresis
- ★ Palpitations (dose dependent)

Common side effects of caffeine

- ★ Nausea
- ★ Headache
- ★ Serious allergic reaction
- ★ Diarrhea
- ★ Vomiting
- ★ Irritability
- ★ Nervousness or anxiety

Side effects of caffeine

Caffeine is likely safe for most adults when used appropriately . Caffeine is possibly unsafe when taken by mouth for a long time or in fairly high doses . Caffeine can cause insomnia,nervousness and restlessness stomach irritation nausea and vomiting increased heart rate and respiration and other side effects.

Caffeine can make sleep disorders in patients with acquired immunode ficiency

Adverse drug reactions (ADR) monitoring from

Preparation of ADR monitoring form as per guidelines given by AMCs (e.g. Indian Pharmacopoeia Commission)

Sr.no	Indian pharmacopeia commission	For AMC /NCC use only
	Report type clinical follow up -	AMC report no -
		World wide unique no -
A	Patient information	12-Relevant test / laboratory data with dates
1	Patient initial	13-relevant medical history (e.g.pregnancy allergy)
2	Age at time event	
3	M-. F-. Other -	
a	Weight. Kg/s	
B	Suspect adverse reactions	14 - serious relations
5	Date of started	☐ Death ☐ Congited
6	Date of recovery	☐ Life threatening
7	Describe reaction problem	☐ Disability
		15-outcome ☐ Recover ☐ RP covering

Suspected medication :

Sr. No	Name (brand) Generic	Manufacturers	Batch No	Exp date	Dose used	Frequency	Route used	Indications casualty Assessment
1								
2								
3								

2 : concentration comitant medical products including medication and herbal remedies with date (exclude those and treatment)

Additional information	D . Reporter details 16- Name professional address Pin-. E-mail - Help No-. (With STD code) Occupation-. Sign- 17-date this report-

Hospital visit :-

Common side effects:-

- difficulty sleeping (insomnia)
- nervousness or anxiety
- irritability
- nausea
- headache

Patient interviewed

Interview of patient for understanding and identification in ADR

- Hospital Name :
- Patient Name :
- Age :
- Disease: abdominal pain, seizures, increased blood acid levels, irregular or fast heartbeat, and reduced blood flow to the heart
- Drug : caffeine

Dosage form:-

- Caffeine oral solution is used to treat short-term apnea of prematurity when premature babies (infants between 28 and 32 weeks gestational age) stop breathing. Apnea of prematurity is caused by the baby's breathing centers not being fully developed.
- Caffeine is available with or without your doctor's prescription.

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