Study of diclofenac drug related with pharmacovigilance

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ABSTRACT

- *Medicines and vaccines have transformed the prevention and treatment of diseases. In addition to their benefits, medicinal products may also have side effects, some of which may be undesirable and / or unexpected. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem.*
  All medicines and vaccines undergo rigorous testing for safety and efficacy through clinical trials before they are authorized for use. However, the clinical trial process involves studying these products in a relatively small number of selected individuals for a short period of time. Certain side effects may only emerge once these products have been used by a heterogenous population, including people with other concurrent diseases, and over a long period of time.
  Diclofenac, a nonsteroidal anti-inflammatory drug, is not a documented cause of rhabdomyolysis in the Summaries of Product Characteristics held by major regulators.
  Diclofenac is a medication used in the management and treatment of inflammatory conditions and pain. It is in the class of non-steroidal anti-inflammatory drugs (NSAID). This activity outlines the indications, mechanism of action, administration, adverse effect profile, contraindications, and other key factors for diclofenac in the clinical setting pertinent to healthcare team members to treat and manage patients with inflammation-related conditions.

Clinical research

- **Definition**

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.

- **Preclinical trials**

Introduction
Details of non-clinical/per-clinical studies are discussed under ICH m3 guidance.
The Non-clinical study recommendations for the marketing approval of a pharmaceutical product include: safety pharmacology studies repeated dose toxicity Studies toxicokinetics and non-clinical pharmacokinetic studies reproduction toxicity studies and genotoxicity studies.
A Typically both In vitro and In Vivo tests will be performed Studies of drug toxicity includes which organs are targeted by that drug, as well if there are any long term Carcinogenic effects or toxic effects causing illness.

- **Phases of preclinical trials**

- **Safety pharmacology :-**

The core safety Pharmacology study includes the assessment of affect cardiovascular, central nervous, respiratory the consideration is given to an any in vivo valuation as addition to general toxicity. Care should be taken to reduce number of animal used

- **Toxicokinetic & Pharmacokinetic studies:-**

In vitro metabolic data for animals and humans & expose data in animals to prior initiating human clinical trials. Further absorption, distribution, metabolism and excretion in animals should be available for treading l
ong duration.

- **Acute toxicity studies:-**

This information has been obtained From single dose toxicity studies in two mammation 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.

- **Respected Dose toxicity:**

In principle the duration of animal toxicity studies conducted in two mammals species.

- **Local Tolerance studies:-**

To evaluate local tolerance by the intended therapeutic bouts as a part of the general toxicity studied. To support limited human adm by non-therapeutic rough eg. (single IV).

- **Genotoxicity studies:-**

An assay for gene mutation is generally considered sufficient to support all single dose clinical development trials.

- **Carcinogenicity studies:-**

It should be conducted for the marketing application.
For pharmaceutical development treat certain serious diseases for adults pediatrics patients carcinogenicity testing.

- **Reproductive toxicity:-**

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 in pregnant women.

- **Other toxicity:-**

Non-clinical study eg. identify potential biomarkers

- **Clinical trials**
- **Introduction**

The clinical trials are the Research studies performed in the people that are aimed at evaluating medical, surgical or behavioral intervention that is called clinical trials.
The evolution of the modern clinical trial dates back at least to the eighteenth century. Lind, in his classical study on board the Salisbury, evaluated six treatments for scurvy in 12 patients. One of the two who was given oranges and lemons recovered quickly and was fit for duty after 6 days. The second was the best recovered of the others and was assigned the role of nurse to the remaining ten patients. Several other comparative studies were also conducted in the eighteenth and nineteenth centuries. The comparison groups comprised literature controls, other historical controls, and concurrent controls.

- **Phases of clinical trials**

1.Phase 0:-
The Phase-0 trials are the exploratory trials that also exist as small clinical trials that involve dosing at a sub-therapeutic level.
Therapy area-any indication
Dosage -sub therapeutic dosing
Trial length -usually Less than one week
It involves 10 to 15 patients

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 is intended to treat.
The Phase-1 has a duration of 1 month to 12 months.
Phase 1 generally involves between 20 to 30 participants.

3.Phase 2:-
phase 2 clinical trials tense detector more about how safe the treatment is and now will it work Doctor also test whether a new treatment works for a specific cancer.
It is approximately 33% of drugs.
The duration is 12 to 24 months.
It involved no more than several 100 participants.

4 Phase 3:-
The main objective of phase 3 is to verify the therapeutic action of a new substance in a large number of patients to determine the risk /benefit reaction.
The duration is 1 to 4 years.
It has 300 to 3000 volunteers involved.

5.Phase 4:-
A type of clinical trials that studies the side effects caused over time by a new treatment after it has been approved and is a market this trious 100k side effects that were not seen in earlier trials that may study how well a new treatment works over a long period.
Its duration is a minimum of two years.
It involves several thousand volunteers who have the disease.

- **Function of Drug Controller General of India (DCGI)**

- **DCGI lays down the standard and quality of manufacturing, selling, import and distribution of drugs in India.**

- **Preparation and maintenance of national reference standards.**
- **To bring about uniformity in the enforcement of the Drugs and Cosmetics Act.**
- **Training of Drug Analysts deputed by State Drug Control Laboratories and other Institutions**
- **Analysis of Cosmetics received as survey samples from CDSCO (central drug standard control organization)**
- **With the notification of Medical Device Rules 2017 by the Government of India, DCGI will also act as Central Licensing Authority (CLA) for the medical devices which fall under the purview of these rules. Out of four Classes of medical devices from Class A to Class D, DCGI will be the direct licensing authority for Class C and Class D devices, whereas it will coordinate licensing for Class A and B devices through State drug controllers, who will act as State Licensing Authority or SLA.**

- **Function of Central Drug Standard Control Organization (CDSCO**

- **Under the Drug and Cosmetics Act, the regulation of manufacture, sale and distribution of Drugs is primarily the concern of the State authorities while the Central Authorities 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 providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.**

- **Types of regulatory application:**

- **Investigational New Drug (IND)**

- **A drug that has not been approved for general use by the food and drug administration but is under investigation in clinical trials regarding its safety and effectiveness first by clinical investigators and then by practicing physicians using patients who have given informed consent to participate.**

- **Duration**

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

- **New Drug Application (NDA)**

- **New Drug Application (NDA)**

The identify and contact information of the sponsor and the phase of the trials. A commitment that an IRB will be responsible for initial and continuing review of The trials. The name of the drug is a list of its active ingredient and its dosage and route of Administration. The objective and planned duration of the proposed clinical trials. Identities and qualifications of all investigators

- **Duration**

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

- **Abbreviated New Drug Application (ANDA**

An abbreviated new drug application ANDA contains data which is submitted to FDA for the review and potentially approval of a generic drug product. Once approved an applicant may manufacture and market the generic drug product to provide a safe,effective,lower cost alternative to the brand name drug it references.

- **Duration**

This act also premises brand name companies to apply for exclusive patient right to cover their new drug for up to 5 years

Goods clinical practice (GCP)

- **ICH GCP**
  - **In the middle part of the last century drug development experience several event that gave weight of greater harmonization within countries initially & then internationally in the U.S a terrible mistake in the formu-**

    lation of children syrup in 1930s forced the American government to initiate the creation of a product authorisation system under the FDA The public expectations for new drug to be both safe & effective come an escalation of cost of research & an ever increasing health care Bill for government.

- **Objective**
  1. **To provide an overview of history of good clinical practice (ICH).**
  2. **To emphaize important of ICH GCP compliance when conducting clinical trials.**
  3. **To recognise implications of non-compliance.**
  4. **To review positive & negative cause studies.**
  5. **Protect the patient.**
  6. **Avoid trials duplication (saving time money resource)**

- **Scope of GCP**

  Good clinical laboratory should be used by all laboratories where test are done on biological specimen diagnosis patient are disease control.
  - **Microbiology & serology**
  - **Hematology & blood banking**
  - **Molecular biology & molecular pathology**
  - **Clinical pathology**
  - **Histopathology**
  - **Studies physiological biochemical process of the response to a**
  - **Specific intervention- whether physics Chemical or physiological in healthy or psychological in healthy or psychological in heating subject in patient**

- **New drug clinical trials rule 2019**
  - **Regulation on biomedical & health research (BH2):**
    Previous studies other than clinical & bio- availability & bioequ
    -ivalent stabilized were not regulated in the drug & cosmetic rule & consequently there was insufficient control on the conduct of this studies these types of studies were covered on the Indian council
    of medical research involving human participants initially in the 2000
    amended in 2006 & 2019 since.
    This was covered only under the Indian council of medical research guide & not under the drug & cosmetic rule.
  - **In new rule 2019 such records has been defined to include studies on basis applied & operational research clinical research designed primary to increase scientific knowledge about disease & it's condition there detection & it's condition there detection & causes & evolving strategy**
    For health promotion prevention or ameliorations of disease & rehabilitation but does not include CT the study type include

  - **In vitro diagnosis (IVDS) Performance testing for research.**
  - **New surgical intervention.**
  - **Assisted reproductive technology (ART).**
  - **public health.**
  - **Epidemiological health survey.**
  - **Observation & non-interventional study of old drugs.**

  - **Rule applicable to biomedical & health research would be applicable from 15 sep 2019**

- **Academic clinical trials**

  - **New rule 2019 describe academic clinical trials as clinical trial of drug already approved for a certain claim initiated clain by any investigator academic or research institute for new indication or now route of administration or new dose or new dosage form.**

- **Ethics committee (ECS)**

  - **As delineated in the 2019 ct rule & additional resource India has decentralized process for the ethical review of clinical trials application & required ethical committee (EC) approved for each trial use.**
  - **In accordance with 2019 ct rules committee (ECS) that review drug clinical trials are required to register with New drug controller general**
    of India (DCGI) head of drug general standard control organization Prior
    To review & approve clinical trial protocol.
  - **In addition the 2019 ct rules established a separate registration & monitoring system for ECS that overase biomedical & health research studies.**
  - **Per notice is sep19 & chapter IV of the 2019 ct rules any institution/organization that plans to conduct biomedical & health research involving human participants is now required to have EC to**
    Review & overase conduct such research before study.
- **EC Composition**

  ∆ The 2019 ct rules & ICMR guidelines, institutional/independent EC
  Should be multidisciplinary multi-sectoral representing mixed
  Gender age composition.
  ∆As per 2019 ct rules ICMR guidelines composition should include
  Following
    - **Chairperson from outside the institute**
    - **One (1) to two(2) basic medical scientist**
      (Performing one (1) pharmacologist)
    - **One (1) two (2) clinical from various institutions.**
    - **Legal experts or retried judge**
    - **One (1) social scientist/ representative**

Non-government voluntary agent
- **One (1) philosopher/ethic**
- **One (1) member independent institutions is non-scientific.**

- **Phase IV & post marketing studies (PMC)**
  - **Previously there was ambiguity define requirements phase IV & PMC new rule 2019 was differentiate requirements conducting phase IV CT & Post marketing surveillance for new drugs.**

- **New rule 2019 phase IV studies**

  - **Drug drug interactions**
  - **Dose response or safe studies**
  - **Trials designed to support use under approved indication**

∆ Post marketing surveillance studies are conducted with new drug Approved condition of it's with scientific objective approved by CLA

- **Orphan Drug registration**

  - **New rule 2019 defines orphan Drug as a drug intended to treat conditions which affect not more than five lakh (500,000) persons in India.**
  - **Provision for post track approval process special status orphan Drug include complete fee waiver CT filling.**
  - **Provision for waiver local clinics study & phase IV on satisfaction of CLA.**
  - **Provision expedited review process in situations where evidence for clinical safety have been established.**

- **Post -trial access**
  - **New rule 2019 defines post trials access as moving New drug investigation New drug available to trials subject after completion of clinical trials through which said drug has been found beneficial to a trial subject during clinical trials.**
  - **There are still some gaps in understanding questions raised about issues needed to address CDSCO.**
  - **How long post trials access medicine should provide to patients is of special importance because there is chronic disease with long treatment.**
  - **How is safety signal monitored for this period? Would sponsor ethics committee.**
  - **Should the sponsor continue to provide drugs under post trials access marketing authorisation approval & drug availability in the market.**

- **Other significant update**

  - **Condition for generally stability data have been revised for drug substance & formulation intended to be stored under general condition for long term from zone IV (A) to zone IV (B) stability data testing condition have been revised as per zone IV (b) for long term from 30°c ±2°c 65% R/+±5% RH+0 3°c ±5% R.H.**
  - **New clinical trials approval timeline also have been included for the clinical trials of drug developed outside of India there as a go working day limit of the CLA to respond**

- **Protocol designing for clinical trials**

  - **Every clinical investigation begins with the development of a clinical protocol. The protocol is a document that describes how clinical trials will be conducted, how the objective (s) design methodology, statistical consideration & organization of a clinical trials & ensure the safety of the trial subject & integrity of the data collected.**
  - **A resource protocol is a document that describes the background, rationale, objective, design, methodology, statistical, consideration & organization of a clinical trials project according to the ICH guidelines a protocol should include the topic.**
    - **Title page (general information)**
    - **Background information**

- **Objective/purpose**
- **Study design**
- **Selection & exclusion of subject**
- **Assessment of efficacy**
- **Assessment of study**
- **Assessment of safety**
- **Adverse effect**
- **Discontinuation of study**
- **Statistics**
- **Ethics**
- **Data heading & record keeping**
- **Publication policy**
- **Project time table**
- **Reference**
- **Supplements/Appendices**

- **Purpose of a research protocol**
    - **Describe the background rationale objective design methodology data analysis & organization of research project.**
    - **A reference to ensure consistent study conduct.**
    - **May be required for IRB or sponsor Approval.**
    - **Source material for writing or other submission reports.**
    - **Consider & describe advance all aspects of a planned study.**

- **Do I need a protocol**
    - **A scientific protocol document is required for CHR review & approval of any greater than minimal risk study.**
    - **Upload as other documents in IRIS.**
    - **A biomedical protocol must be GCP**
    - **International ethical & scientific quality standards for research involving human.**

Concept of pharmacovigilanace

- **Definition objective, types & components of pharmacovigilanace**

- **Definition**

  Pharmacovigilance is the science & activities relating to the detection Assessment, understanding & prevention of adverse effect or any other medicines related problem for patient safety.

- **Objective**

- **Improvement of patients care & safety in relation to the use of medicine with medical & paramedical intervention remain to be an important parameters.**
- **The main objective of PV involve exciting the efficacy of drug by monitoring their adverse effect profile for many years from the lab to the pharmacy tracking & drastic effect of drug improving public health & safety relation to**

- **Types**
- **There are four important type in pharmacovigilance.**

    1. **Passive surveillance**
    2. **Active surveillance**
    3. **Cohort event monitoring**
    4. **Targeted clinical investigation**

1. **Passive surveillance:**
   - **Passive surveillance method involves the usage of spontance adverse event reports voluntarily sent by health care professionals for patients to the marketing authority.**
   - **The data related to the adverse reactions are collected in a central or regional data.**

2. **Active surveillance :**

   - **This method aims to monitor certain specific drug related ade & seeks to certained the number of ADR entirely through a pre-planned process.**
   - **It is commonly known as toxicity monitoring or safety monitoring.**

3. **Cohort event monitoring:**

   - **In this method the study is planned Prior to beginning the treatment with the medication.**
   - **A group of people are exposed to a drug for a defined period & actively followed up during treatment.**

4. **Targeted clinical investigation:**

   - **These kinds of investigations are performed to identify and characterize the adverse reactions related to a drug among special populations like people with some genetic disorder, pregnant women & older people.**

- **Components**

1. **Adverse events case management including expedited report**

- **European union :**
  Fact- EU Pharmacovigilanace laws means that all spontaneous report regarding serious adverse reactions must be expendiated within 15 days in addition as 22nd November 2019 all non-serious adverse reactions with an origin within EU required expending to within 90 days

- **EXPEDITED REPORTING:**
  L Involve a serious and unlisted event. The timeframe for reporting expedited cases 7/15 calendar days Within clinical trials - SUSAR (a Suspected Unexpected Serious Adverse Reaction). SUSAR, life-threatening or fatal, subject to a 7-day "clock".
- **Post marketing phase:**
  Any clinical trials including post-authorization studies during the post-marketing phase of a product will need to be correctly processed and expedited according to regulatory requirements

2. **Aggregate reporting :**
   Aggregate reporting is the process that reviews the cumulative safety information from a wide range of sources, on a periodic basis and submits the findings to regulators worldwide.

   The aggregate safety reports are presented to regulators as soon as the medicine is marketed anywhere in the world and enables understanding of risk and benefit profile of the product over a period of time

   These reports focus not so much on individual cases, but rather on overview, assessment of the safety profile and benefit-risk-evaluation of Adverse Drug Reaction (ADR) and the Serious Adverse Event (SAE) and pregnancy reports.

- **Why is aggregate reporting important?**

  Though the Individual case safety reports were submitted on expedited basis to regulatory authorities, detailed analysis and evaluation of the benefit/risk ratio of a drug is not possible at

this level. Therefore periodically reviewing safety reports received cumulatively worldwide, becomes significant to analyze the benefit/risk balance of the product

These reports need special diligence and attention to

detail on the one hand, overview and a sense of what

is essential on the other hand

- **Types of aggregate reports**

1. Pre-marketing report

- **IND annual reports**
- **• Clinical study reports (CSR)**
- **• Development Safety Update Report (DSUR)**
- **Annual safety reports (ASRS) in Europe**

2. Post-marketing report

- **Periodic Benefit Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR)**
- **Periodic Adverse Drug Experience Report**
- **(PADER) • NDA and ANDA annual reports**
- **Addendum to clinical overviews (ACO)**

3. Signal intelligence

- **Signal detection in Pharmacovigilance involves looking at the adverse reaction data for patterns that suggest new safety information. This page provides a brief introduction to the definition and purpose of signals and some of the key methodologies employed.**
- **What Is A Signal?**
  The term is most commonly associated with drugs during the post-marketing phase, although it may also be used during pre-marketing clinical trials.
- **Signal Management in Pharmacovigilance?**
  The process of signal management in pharmacovigilance is a set of activities which aim to determine:
  whether there are new risks associated with a particular drug, or
  whether risks associated with a particular drug have changed
  Sources for the detection of signals can come from.
  - **spontaneous reporting**
  - **active monitoring systems**
  - **interventional studies (clinical trials)**
  - **non-interventional studies (pharmacoepidemiology studies)**
  - **non-clinical studies (e.g. animal toxicology studies)**
  - **systematic reviews (i.e. thorough review of the published literature)**
  - **meta-analyses (i.e. mathematical pooling of all the clinical trial data)**
  - **other relevant sources**

4. Risk management

- **A medicinal product is authorized on the basis that in the specified indication(s), at the time of authorisation, the risk-benefit is judged positive for the target population. However, not all actual or potential risks will have been identified when an initial**

authorisation is sought. In addition, there may be subsets of patients for whom the risk is greater than that for the target population as a whole.

- **Risk management in pharmacovigilance is undertaken to promote safe use of medicines and safeguard health of patients.**

- **Risk management legal framework**
  - **Safety specifications**
  - **Pharmacovigilance plan**
  - **Risk minimisation plan**
  - **Management of single of risk**

1. **Risk detection**
2. **Risk assessment**
3. **Risk minimisation**
4. **Risk communication**

- **Constitution objective of PV of India**
  - **The purpose of the Pharmacovigilance Program of India is to collect, collate and analyze data to arrive at an inference to recommend regulatory interventions, besides communicating risks to healthcare professionals and the public.**

  - **The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in collaboration with Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi has launched the nation-wide Pharmacovigilance programme for protecting the health of the patients by ensuring drug safety. The programme is coordinated by the Department of Pharmacology at AIIMS as a National Coordinating Centre (NCC). The center will operate under the supervision of a Steering Committee.**

  - **Objective :**
    - **To monitor Adverse Drug Reactions (ADRs) in Indian population**

    - **To create awareness amongst health care professionals about the importance of ADR reporting in India**

    - **To monitor benefit-risk profile of medicines**

    - **Generate independent, evidence based recommendations on the safety of medicines**

    - **Support the CDSCO for formulating safety related regulatory decisions for medicines**

    - **Communicate findings with all key stakeholders**

    - **Create a national center of excellence at par with global drug safety monitoring standards**

- **List of national adverse drug monitoring center (AMCS) & their function**

  - **Department of Pharmacology, All India Institute of Medical Sciences, New Delhi. (co-ordinator -Dr. Y.K. Gupta National Coordinator)**

- **ADR Monitoring Centres (AMC)**

  1.Department of Pharmacology, &nbs   Therapeutics & Toxicology, Govt. Medical College, Bakshi Nagar, Jammu.
  (Co-ordinator -Dr. Vishal Tandon)

2. Department of Pharmacology, PGIMER, Chandigarh
(Co-ordinator -Dr. Bikash Medhi)

3. Department of Pharmacology, R.G. Kar Medical College, Kolkata
(Co-ordinator Dr. Anjan Adhikari)

4. Department of Pharmacology, Lady Hardinge Medical College, New Delhi
(Co-ordinator -Dr. H.S. Rehan)

5. Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, Parel, Mumbai
(Co-ordinator -Dr. Urmila Thatte)

6. Department of Clinical & Experimental Pharmacology, School of Tropical Medicine, Chittaranjan Avenue, Kolkata
(Co-ordinator -Dr. Santanu Tripathi)

7. Department of Pharmacology, JIPMER, Pondicherry
(Co-ordinator -Dr. C Adithan)

8. Department of Clinical Pharmacy, JSS Medical College Hospital , Karnataka
(Co-ordinator -Dr. Parthasarathi G)

9. Department of Pharmacology , Medical College , Guwahati. Assam
(Co-ordinator -Dr. Mangala Lahkar dr_mlahkar)

10.Institute of Pharmacology , Madras Medical College, Chennai
(Co-ordinator -Dr. R Nandini)

11.Department of Pharmacology, SAIMS Medical College Indore-Ujjain (Co-ordinator -Dr. Chhaya goyal)

12.Department of Pharmacology, GSVM Medical College, Swaroop Nagar, Kanpur, U.P.
(Co-ordinator -Dr SP Singh)

13.Department of Pharmacology, Pandit Bhagwat Dayal Sharma, Post Graduate Institute of Medical Sciences, Rohtak, Haryana.
(Co-ordinator -Dr MC Gupta)

14.Department of Pharmacology, Dayanand Medical College and Hospital, Ludhiana, Punjab
(Co-ordinator -Dr. Sandeep Kaushal)

15. Department of Clinical Pharmacology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, J&K.
(Co-ordinator -Dr. ZA Wafai)

16.Himalayan Institute of Medical Sciences, Dehradun, Uttrakhand
(Co-ordinator -Dr. DC Dhasmana)
17.Department of Pharmacology, Santosh Medical University, Santosh Nagar, Ghaziabad
(Co-ordinator -Dr VC Chopra)

18. Department of Pharmacology, SMS Medical College , Jaipur
(Co-ordinator -Dr. Mukul Mathur)

19.Department of Clinical Pharmacology, Christian Medical College,Vellore, Tamil Nadu

(Co-ordinator -Dr. Sujith chandy)

- **Function of AMC**
    - **To monitor ADR.**
    - **To optimize safe & effective use of medicine in our set up.**
    - **To create awareness amongst health care professionals about the importance of ADR reporting.**
    - **To monitor the benefit risk profile of medicine.**
    - **Generate independent, evidence based recommendations on safety medicine.**
    - **Support the CDSCO for formulation safety related regulatory decisions for medicine.**
    - **Communicate finding with all key stakeholders.**
    - **Create a national center of excellence as per with global Drug safety monitoring standards.**

Safety monitoring during clinical trial

- **Keywords: contraindications, indication , Efficacy, safety, pharmacokinetic of diclofenac**

- **Diclofenac**

- **Introduction**

❖ **Diclofenac is a non-steroidal anti- inflammatory drug(NSAID).This medicine works by reducing substances in the body that cause pain & inflammation.**

❖ **Diclofenac is used to treat mild to moderate pain,or signs & symptoms of osteoarthritis or rheumatoid arthritis.**

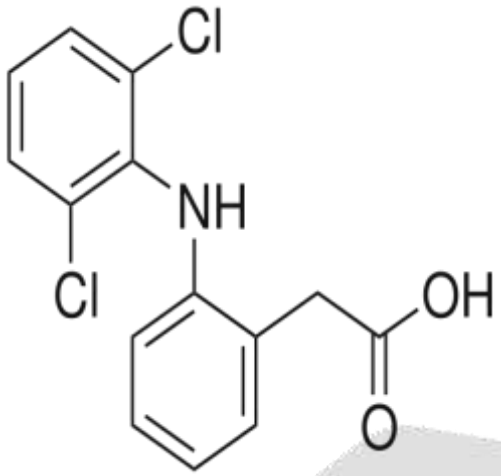
- **Brand**
- **Cataflam**
- **Voltaren-XR**
- **Cambia**
- **Zipsor**
- **Zorvolex**

- **Uses**

  The enteric-coated tablet form of diclofenac is used to reduce pain, swelling (inflammation), and joint stiffness from arthritis. Reducing these symptoms helps you do more of your normal daily activities.Diclofenac is known as a nonsteroidal anti-inflammatory drug (NSAID). It works by blocking your body's production of certain natural substances that cause inflammation. This effect helps to decrease swelling, pain, or fever.Ask your doctor about non-drug treatments and/or using other medications to treat your pain.

- **Route of administration**
- **Oral**
- **Intramuscular**
- **Intravenous**
- **Transdermal**
- **Rectal**

- **Structure**



- **Discovery & development**
- **Diclofenac was patented in 1965 by Ciba-Geigy; it came into medical use in the United States in 1988.**
- **Diclofenac sodium was synthesized by Alfred-sallmann &Rudolf Pfister & First introduced by ciba-geigy.**
- **The purpose of developing diclofenac sodium was synthesized as non-steroidal anti-inflammatory drugs with high activity and outstanding tolerability.**
- **The elements of structure are based on analysis of other non-steroidal anti-inflammatory drugs.**
- **The results of diclofenac sodium which has an acidity constant of 4.0& partition coefficient of 13.4.**
- **The structural element include a phenylacetic acid group a secondary amino group & phenyl ring contain chlorine atoms**

- **Preclinical research**
- **Experiments on labeling of diclofenac, an anti-inflammatory drug, with 99m Tc were performed. High (about 96%) yield of 99m Tc-diclofenac is reached under the following conditions: 50 μg of Sn(II), 100 μg of the substrate, 30 min, pH 7. 99m Tc-diclofenac was stable for 4 h. Biological distribution of 99m Tc-diclofenac was investigated in mice bearing inflammations experimentally induced in the left thigh by Escherichia coli (bacterial infection model) and turpentine oil (sterile inflammation model). The uptake ratio in the inflamed and contralateral thighs (target-to-nontarget, T/NT) was evaluated. In the case of bacterial infection, the T/NT ratio only slightly exceeds unity, whereas in the case of sterile inflammation it reaches 4.46 ± 0.07 in 2 h. Thus, 99m Tc-diclofenac allows differentiation between septic and aseptic inflammation and can be recommended for further clinical trials.**

- **Clinical trials**
- **In an open, comparative multicentre trial, 96 patients with arthritis of the large joints were treated with 75 mg diclofenac in one single dose in the morning, 50 mg diclofenac given twice daily, or 250 mg naproxen administered twice a day. It was noted that the length of history of pain was significantly longer in this naproxen group. Duration of the study was 14 days. Clinical parameters showed that the best degree of improvement was obtained with the diclofenac 50 mg twice-daily dosage regime. Diclofenac, in this study, showed better tolerability than naproxen.**

- **NSAIDs are commonly used in the management of acute pain; Diclofenac is one from the same class. It is an amino phenyl acetic acid derivative which inhibits prostaglandin biosynthesis to produce analgesic, antipyretic and anti-inflammatory effects. The drug efficacy and safety in acute pain management has been proved by several studies like in renal colic, post and pre-operative pain management, migraines etc. It's also known to have an opioid-sparing effect. Mode of administration is one of the important factors to consider in a busy emergency room. Perception about the route of administration differs among patients. As believed,injectables have rapid onset, are easier to titrate, and patients respond better to them as they consider them stronger than oral medication. Number of trials has compared oral and parenteral NSAIDs. Most found no benefit to the parenteral route. Considering the limitations of the previously done**

studies like small sample size, heterogeneity in the group of patients enrolled, improper blinding and comparing of two different drugs from the same class. Therefore, aim of the study is to conduct a Double blind randomized clinical trial to assess the clinical efficacy and pharmacokinetic parameters of oral diclofenac compared to intramuscular diclofenac in patients with acute limb injury.

- **In this two group double blind randomized clinical trial, the clinical efficacy and pharmacokinetic parameters among the two groups will be assessed. Eligible patients visiting to HGH-ED, age (above 18 years) with acute limb injury, having moderate to severe pain (defined as pain score of >=4 on Numerical rating scale) will be recruited. With the use of computer generated block randomization, subjects will be allocated to one of the two treatment groups in the ratio of 1:1. Each group will receive either (intramuscular diclofenac / oral placebo) or (oral diclofenac / intramuscular placebo). Among the 300 subjects enrolled for the study, further stratified randomization will be done in order to enroll 20 patients for pharmacokinetic study within the subjects.High-performance liquid chromatography, method will be used for the determination of drug concentration in human plasma, for detailed pharmacokinetics. The pain score will be assessed by using the validated pain scale i.e. Numerical rating scale (NRS). The participants, clinicians and investigators will be masked to treatment assigned and the results will be analyzed by the intention to treat analysis among the two group treatments.**

- **Pharmacokinetic (ADME)**
- **Absorption:**

  Diclofenac is 100% absorbed after oral administration compared to IV administration as
  measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available (see Table 1). Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption of 1 to 4.5 hours and a reduction in peak plasma levels of <20%.
- **Distribution:**

  The apparent volume of distribution (V/F) of diclofenac sodium is 1.4 L/kg. Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15-105 µg/mL) achieved with recommended doses.
  Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.
- **Metabolism:**

  Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxy- and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects. However, diclofenac metabolites undergo further glucuronidation and sulfation followed by biliary excretion.
  One diclofenac metabolite 4'-hydroxy- diclofenac has very weak pharmacologic activity.
- **Excretion:**

  Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 2 hours

- **Pharmacodynamic**

- **Diclofenac reduces inflammation and by extension reduces nociceptive pain and combats fever. It also increases the risk of developing a gastrointestinal ulcer by inhibiting the production of protective mucous in the stomach**

- **Indication**

  Diclofenac is an FDA-approved drug used in the treatment and management of acute and chronic pain associated with inflammatory conditions, especially those involving the musculoskeletal system. These include osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Topically, it can treat actinic keratosis.[1][2] Diclofenac is also FDA approved for ophthalmic administration for the extraction of cataracts, pain in the eye, and photophobia. It is a non-steroidal anti-inflammatory drug (NSAID) and, although it can help to manage the symptoms of pain during inflammatory processes, it cannot reverse or prevent chronic joint damage seen with osteoarthritis and rheumatoid arthritis. Diclofenac was synthesized in 1973 and is the most widely prescribed NSAID worldwide.[3][4]

  Diclofenac has been used off-label to treat biliary colic, corneal abrasion, fever, gout, migraine, myalgia, and post-episiotomy pain. Diclofenac 1% gel was approved for over-the-counter distribution in February 2020 for the management of arthritic pain. Otherwise, diclofenac is only available via prescription.

  Studies have also elucidated the benefits of using diclofenac post-operatively to reduce the need for rescue analgesia in patients after surgery.[5]

- **Contraindications**
  Like other selective COX-2 inhibitors, diclofenac is contraindicated with an FDA boxed warning in patients with a history of increased cardiovascular risk such as MI or stroke. Diclofenac should not be used in bypass graft surgery of coronary artery due to a higher risk of MI and stroke. Diclofenac is also listed as a Beers list drug and should be avoided in elderly patients due to potential adverse effects involving the cardiovascular and gastrointestinal systems.[18] It is also contraindicated in patients with a history of anaphylactoid reaction to NSAID drugs.

  Also, diclofenac is contraindicated in patients with mild or severe renal insufficiency due to potential negative effects of decreased renal perfusion. Clinicians should not use diclofenac or other NSAIDs in patients with a history of GI bleeds or ulcerations. Special monitoring is a consideration in patients with a history of Helicobacter pylori infection. Formulations of diclofenac with misoprostol are contraindicated in pregnant females due to possible side effects involving loss of pregnancy associated with misoprostol.[19][20]

- **Toxicology**

  Symptoms of overdose include lethargy, drowsiness, nausea, vomiting, and epigastric pain, and gastrointestinal bleeding.Label Hypertension, acute renal failure, respiratory depression and coma occur rarely. In case of overdose, provide supportive care and consider inducing emesis and administering activated charcoal if overdose occurred less than 4 hours prior.
  Acute diclofenac induced toxicity in hepatocytes was preluded by a decrease in ATP levels whereas no significant oxidative stress (decrease in glutathione & lipid peroxidation) or increase in intracellular calcium concentration could be observed at early incubation stage
  In-vitro cytotoxicity well with the formation by hepatocytes of 5-hydroxydiclofenac
  The experiment results suggest that the toxic effect of diclofenac on hepatocytes may be caused by drug induced mitochondrial impairment

- **Genotoxicity**
  The genotoxic potential of Diclofenac Sodium (DC) in terms of induction of chromosomal aberration (CA), micronucleated polychromatic erythrocytes (MNPCE) in bone marrow and sperm abnormality in germ cell of mice has been investigated in Swiss albino mice (Mus musculus). Cyclophosphamide (CP) 40 mg/kg was used as clastogenic in positive control while

multiple doses of DC (1.5, 2.5 and 3.5 mg/kg) were given orally in test groups. Bone marrow and germ cells were sampled at 4, 13, 26 and 40 weeks after treatment. Significant structural chromosomal aberrations and sperm abnormalities were induced with all the selected doses at after 26 and 40 weeks exposure. Also a significant number of MNPCEs were produced with higher dose (3.5 mg/kg) after the a period of 13, 26 and 40 weeks as the chromosomal fragments produced ended up as micronuclei. The PCE/NCE ratio and the mitotic index decreased indicating that DC prevents cell division in mouse bone marrow. Thus, it can be concluded that prolonged use of Diclofenac sodium at high doses is genotoxic in both somatic cells as well as the germinal cells of mice.

- **Safety pharmacology**

  Diclofenac sodium is the active ingredient in Voltaren, a nonsteroidal anti-inflammatory drug designed by selection of appropriate physicochemical and steric properties. Its pharmacologic activity, specifically its effects in acute and subchronic inflammation, and its analgesic activity have been assessed in animal models. The tolerability of the compound as judged by several parameters (i.e., ratio between the acute lethal dose or the dose inducing gastrointestinal blood loss and the desired pharmacologic activity) is favorable in comparison with other nonsteroidal anti-inflammatory drugs, Diclofenac sodium acts by potent cyclo-oxygenase inhibition, reduction of arachidonic acid release, and enhancement of arachidonic acid uptake. It thereby results in a dual inhibitory effect on both the cyclo-oxygenase and lipoxygenase pathways.

- **Efficacy of Drug**
- **Diclofenac is effective in treating acute chronic pain & inflammatory conditions; it shows good pain control & has good analgesic effectiveness after extraction .**
- **The name diclofenac is derived from Chemical name dichlorophenyl acetic acid.**
- **Non-steroidal anti-inflammatory drugs are one of the treatment options to be used as pain relief.**

- **Reproductive toxicology**

  Although there are several reports on the toxic actions of sodium diclofenac (DF), there is dearth information on its effect on the male reproductive system. Therefore, the study investigated the effects of DF and melatonin in male rats. Twenty rats were used in this study, which lasted for 6 weeks. The control group (vehicle treated) received normal saline (0.1 ml/day, p.o.). In the experimental groups, DF was administered during the first (group 2) and last (group 3) three weeks of the study. However, in group 4, melatonin was administered for 3 weeks, after 3 weeks of treatment with DF. DF and melatonin were administered at 1 and 10 mg/kg b.w./day (p.o.) respectively. The results showed that unlike melatonin, DF had no effect on gonadotropins; however, it caused significant decreases in GNRH and testosterone, but a significant increase in prolactin. Melatonin attenuated the pro-antioxidant and pro-inflammatory effects of DF, which caused significant decreases in SOD, TAC, CAT, but significant elevations in LDH, MDA, uric acid and CRP. Moreover, the hormone reversed the adverse effect of DF on sperm count, sperm motility and sperm morphology. There was slight evidence of the precipitation of imbalance in lipid metabolism by DF and the antidyslipidemic action of melatonin. Compared to DF, DF recovery showed more adverse effects on prolactin, testosterone, LDH, MDA, UA, CRP, semen parameters (except sperm motility), TC, LDL-c, HDL-c and phospholipid. The histological results agreed with the biochemical assays. In conclusion, the reproductive toxicity effects of DF seem to escalate after withdrawal; however, these effects could be attenuated by treatment with melatonin.

- **Drug drug interactions**
  - **Diclofenac & alcohol & food interaction:**

    :Ask your doctor before using diclofenac together with ethanol. Do not drink alcohol while taking diclofenac. Alcohol can increase your risk of stomach bleeding caused by diclofenac. Call your doctor at once if you have symptoms of bleeding in your stomach or intestines. This includes black, bloody, or tarry stools, or coughing up blood or vomit that looks like coffee grounds. It is important to tell your

doctor about all other medications you use, including vitamins and herbs. Do not stop using any medications without first talking to your doctor.

- **Diclofenac Disease Interactions:**
  There are 12 disease interactions with diclofenac.

1. **Asthma**
2. **Fluid retention**
3. **GI toxicity**
4. **Rash**
5. **Renal toxicity**
6. **Anemia**
7. **Heart failure**
8. **Hypertension**
9. **Hepatotoxicity**
10. **Platelet aggregation inhibition**
11. **Porphyria**
12. **Hyperkalemia**

- **Diclofenac is a nonsteroidal anti-inflammatory drug. (NSAID). Do not combine it with other NSAIDs unless directed by your doctor.**

- **Examples of other NSAIDs are:**

★ **ketorolac**
★ **ibuprofen**
★ **naproxen**
★ **aspirin**
★ **celecoxib (Celebrex)**
★ **dexketoprofen**

- **Investigator**
  - **Investigation of the immunogenicity of diclofenac and diclofenac metabolites:**

Oral administration of the non-steroidal anti-inflammatory drug diclofenac (DCF) is associated with a high incidence of adverse drug reactions, some of which are thought to be mediated by the immune system. It has been proposed that metabolic activation of DCF and covalent binding to protein generates an antigenic determinant that stimulates immune cells; however, the nature of the metabolite remains ill-defined. The aim of this study was to synthesize and evaluate the antigenic potential of DCF metabolites in the mouse. DCF and DCF metabolites were administered via subcutaneous injection over a 5-day period to BALB/C strain mice to induce immune activation. Proliferation was measured by the addition of [(3)H] thymidine to ex vivo isolated draining auricular lymph node cells. Results were compared with those provoked by exposure to 2,4-dinitrochlorobenzene. Lymph node activation was observed following treatment with 2,4-dinitrochlorobenzene, 5-hydroxy DCF quinoneimine and 4'-hydroxy DCF quinoneimine, but not DCF acyl glucuronide or DCF itself. Interestingly, lymph node cells from 5-hydroxy DCF-treated mice were also found to proliferate, when compared with cells from vehicle-treated mice, while 4'-hydroxy DCF did not stimulate lymph node cell activation. The reactivity of 5-hydroxy DCF quinoneimine was confirmed by synthesis and characterization of an N-acetyl cysteine adduct. These data show that formation of 5-hydroxy DCF and subsequent autoxidation provides an antigenic determinant for immune cell activation in the mouse.

Selection of drug class

- **Selection of drug class for pharmacovigilance study using different criteria. (Eg-commercial availability, selling of drug)**

- **Availability**
- **Diclofenac are available for following forms**
    - **Tablet**
    - **Solution**
    - **Injection**
    - **Gel**

- **It is a non-steroidal anti-inflammatory drug available in all counter**

- **Available**

- **Diclofenac is available under the following different brand names:**

- **Cataflam**
- **Voltaren-XR**
- **Cambia**
- **Zipsor**
- **Zorvolex**

- **Selling of drug**

- **Diclofenac is frequently used with opioids like codeine. Ciba-Geigy patented Diclofenac in 1965, and Ciba-Geigy (now Novartis) manufactured and marketed Diclofenac as Voltaren by GSK in 1973. It was first used in medicine in the United States in 1988.**
- **Furthermore, Diclofenac received FDA clearance in 2007 for the management of pain associated with osteoarthritis of the joints that respond to topical treatment. It was prescribed for the treatment of joint pain in the hands, knees, and feet.**
- **Diclofenac belongs to the non-steroidal anti-inflammatory medicine (NSAID) class of drugs (NSAID). They work by decreasing hormones that cause inflammation and pain in the body. Diclofenac gel, when applied to the skin, has the same effect as a tablet or capsule. Diclofenac can be taken orally, rectally via a suppository, injected, or administered topically**

- **Cost of Diclofenac**

- **Diclofenac HPMC films presented a faster drug release and a higher drug penetration than nanoparticles; on the contrary nanoparticles containing films were able to give a more sustained release of the drug and thus a slower diclofenac permeation through the cornea than HPMC films.**
- **Pyrrolidine dithiocarbamate inhibits mouse acute kidney injury induced by diclofenac by targeting oxidative damage, cytokines and NF-κB activity:**
    - **We observed that diclofenac increased proteinuria and urine neutrophil gelatinase-associated lipocalin (NGAL), blood levels of urea, creatinine, oxidative stress, C-reactive protein (CRP), and pro-inflammatory cytokine after 24 h of a bolus administration. In renal tissue, diclofenac also induced morphological changes consistent with kidney damage, modulated cytokine production, increased oxidative stress and reduced antioxidant defenses. These alterations induced by diclofenac were accompanied by activation of NF-κB in the kidney. Treatment with PDTC dose-dependently reduced diclofenac-induced blood urea, creatinine, and oxidative stress. In addition, PDTC reduced proteinuria and urine NGAL levels and blood CRP and pro-inflammatory cytokines. In the kidney, PDTC inhibited diclofenac-induced morphological changes, pro-inflammatory cytokine production, oxidative stress, and NF-κB activation, and increased antioxidant defenses and anti-inflammatory cytokine IL-10.**

- **Profiling of selection drug class**

  (Eg-MOA, pharmacological effect,ADR, drug interactions, contraindications)
- **(Above the point information are already mentioned in module no: 4)**

Consumption report

- **Top drug rank - 72**

Estimated number of prescription in U.S (2020)	**9.926.749**
Estimated number of patients in the U.S (2020)	**3.647.127**

- **Average total drug costs (USD)**

Per prescription	**$73.57**
Per day therapy	**$10.28/day**

- **Average out of-pocket cost (USD)**

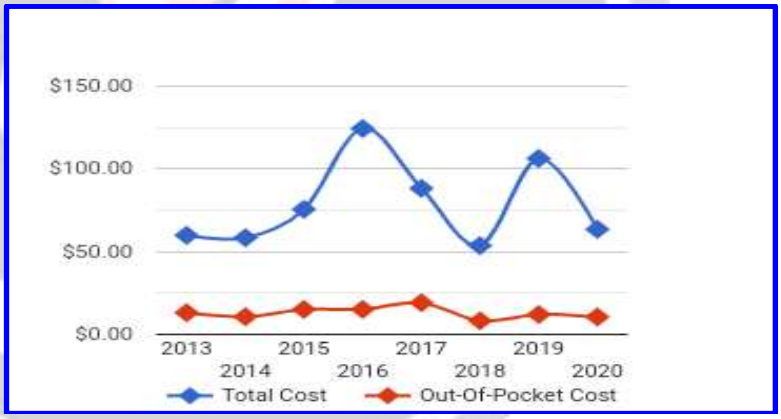
Per prescription	**$10.49**
Per day therapy	**$0.94/day**

- **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.**

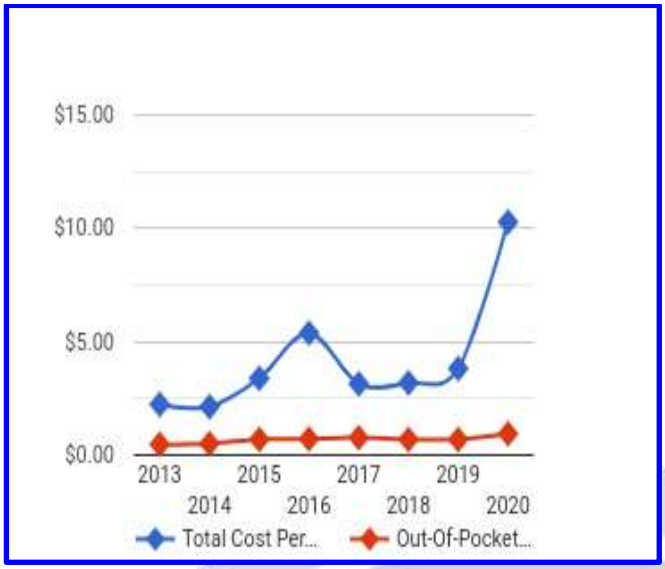
Year	Rank	Change
2013	**73**	**⬆□7**
2014	**84**	**⬇□11**
2015	**84**	**0**
2016	**80**	**⬆□4**
2017	**101**	**⬇□21**
2018	**81**	**⬆□20**
2019	**74**	**⬆□7**

2020	**72**	**↑□7**

- **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 (e.g. 10 days, 30 days, 90 days, etc.)**
  - **Cost per Day of Therapy: The average cost per prescription fill divided by the days of therapy. For example, a 10-day antibiotic course costing $30 would be $3 per day. Similarly, a 30-day supply of an oral antihypertensive costing $30 would be $1 per day.**
  - **Total cost: The 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-pocket cost: The average payment made by the patient which may include deductibles, coinsurance, copayments, or the cash price paid without insurance coverage**



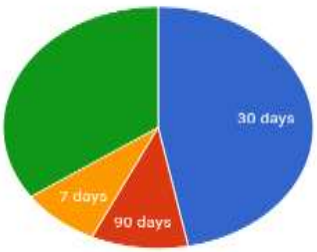
- **Cost per prescription fill(USD)**



- **Cost per day of therapy (USD/Day)**
- **Distribution of dispensed dosage forms (2020)**

Dosage form	Strength	%of dispensed product
Gel	1%	48.5%
Tablet	75mg	36.2%
Tablet/capsule	50mg	13.7%
Other unspecified,or miscellaneous		1.6%

- **Distribution of drugs supply (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.**



- **Therapeutic classes**

- **Central Nervous System Agents**
- **Analgesics**
- **Nonsteroidal Anti-inflammatory Agents**
- **Topical Agents**
- **Dermatological Agents**
- **Topical Non-steroidal Anti-inflammatories**

- **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.**

- **Generic drug synonyms & salts**

  - **Diclofenac Epolamine**
  - **Diclofenac Potassium**
  - **Diclofenac Sodium**
  - **Diclofenac**

- **FDA Approval information**

Established Pharmacologic Class (EPC):	**Non-steroidal anti-inflammatory drugs**
Initial FDA Approval date	**28-07-1988**
Frist FDA applicant	**Discn**
Frist dosage forms	**Tablet delayed released (oral)**

Identification of adverse effect of selected drug

- **Diclofenac**

  - **Generic name: diclofenac**
  - **Brand name:**
    cambia, zorvolex, cataflam,voltaren,dyloject

  - **Drug class: non-steroidal anti-inflammatory drug**

- **Warning**

  - **You should not use diclofenac if you have a history of allergic reaction to aspirin or NSAIDs (non-steroidal anti-inflammatory drugs).**

  - **Diclofenac can increase your risk of fatal heart attack or stroke, especially if you use it long term or take high doses, or if you have heart disease. Do not use this medicine just before or after heart bypass surgery (coronary artery bypass graft, or CABG).**

  - **Diclofenac may also cause stomach or intestinal bleeding, which can be fatal. These conditions can occur without warning while you are using this medicine, especially in older adults.**

- **Before taking this medicine**

- **Diclofenac can increase your risk of fatal heart attack or stroke, even if you don't have any risk factors. Do not use this medicine just before or after heart bypass surgery (coronary artery bypass graft, or CABG).**

- **Diclofenac may also cause stomach or intestinal bleeding, which can be fatal. These conditions can occur without warning while you are using this medicine, especially in older adults.**

- **You should not use diclofenac if you are allergic to it, or if you have ever had an asthma attack or severe allergic reaction after taking aspirin or an NSAID.**

- **Do not use Cambia to treat a cluster headache. Do not use Zipsor if you are allergic to beef or beef protein.**

- **To make sure this medicine is safe for you, tell your doctor if you have:**

    - **heart disease, high blood pressure;**
    - **ulcers or bleeding in your stomach;**
    - **asthma;**
    - **liver or kidney disease; or**
    - **if you smoke.**

- **Side effect of diclofenac**

    - **Get emergency medical help if you have signs of an allergic reaction to diclofenac (hives, difficult breathing, swelling in your face or throat) or a severe skin reaction (fever, sore throat, burning eyes, skin pain, red or purple skin rash with blistering and peeling).**

    - **Stop using diclofenac and seek medical treatment if you have a serious drug reaction that can affect many parts of your body. Symptoms may include skin rash, fever, swollen glands, muscle aches, severe weakness, unusual bruising, or yellowing of your skin or eyes.**

    - **Get emergency medical help if you have signs of a heart attack or stroke: chest pain spreading to your jaw or shoulder, sudden numbness or weakness on one side of the body, slurred speech, feeling short of breath.**

    - **Stop using this medicine and call your doctor at once if you have:**

    - **the first sign of any skin rash, no matter how mild;**

        - **flu-like symptoms;**
        - **heart problems - swelling, rapid weight gain, feeling short of breath;**
        - **kidney problems - little or no urinating, painful or difficult urination, swelling in your arms or legs, feeling tired or short of breath;**
        - **liver problems - nausea, diarrhea, stomach pain (upper right side), tiredness, itching, dark urine, jaundice (yellowing of the skin or eyes); or**
        - **signs of stomach bleeding - bloody or tarry stools, coughing up blood or vomit that looks like coffee grounds.**

- **Common diclofenac side effects may include:**

    - **indigestion, gas, nausea, vomiting, stomach pain;**
    - **diarrhea, constipation;**
    - **headache, dizziness, drowsiness;**
    - **abnormal lab tests;**
    - **itching, sweating;**
    - **stuffy nose;**

- **increased blood pressure; or**
- **swelling or pain in your arms or legs.**

Adverse drug reactions monitoring form

Indian pharmacopeia commission	**For AMC NCC Use only**
A- patients information;	**AMC report no:**
1.patient initial	**World wide unique no:**
2.age at time event	**12 .Relevant test laboratory data with dates**
3.M •F. •Other	**13. Relevant medical medication history E.g-Pregnancy Allergy**
4.weight-. Kgs	**14.Seriousness of reactions • Yes-. • No-**
B-suspected adverse reactions:	**•Death-. • Congenital anomaly-**
5.Date of reactions store	**•Life threatening -. •Other specific-**
6.Date of recovery	**•Disability-**
7.Describe reaction or problem	**•Recovered-. •Recovering unknown**

C-suspected medication:

Sr.no	**Name (Brand) Generic**	**Manufa-cturer**	**Batch No**	**Exp Date**	**Dose Used**	**Freque-ncy**	**Route Used**	**Indicati-on**
1.								
2.								
3.								

Action taken (please tick) Drug withdraw dose increase dose Decrease	**Reactions reappeared •Yes-. •No-. •Effect unknown**

- **Comitant medical product including self herbal remedies with therapy date (Exclude those used to use treatment)**

•Additional information	**0. Reporter details**

	16.Name & professional address **•pin-. •Email-** **(Tel no). (With STD code)** **•occupation-** **•Signature-** **17.Date of this report**

Hospital visit

- **Common side effect**
    - **feeling sick (nausea)**
    - **being sick (vomiting) or diarrhea.**
    - **feeling dizzy or vertigo.**
    - **headaches.**
    - **stomach ache, wind or loss of appetite.**
    - **mild rash.**
- **Serious side effect**
    - **Diclofenac tablets and capsules can cause an ulcer in your stomach or gut if you take them for a long time or in big doses.**
    - **There's also a small risk of heart failure or kidney failure if you take very big doses (150mg a day) for a long time.**
    - **It's best to take the lowest dose that works for the shortest possible time.**
- **Serious allergic reaction**
    - **Call your doctor right away if you have a rash, itching, trouble breathing or swallowing, or any swelling of your hands, face, or mouth while you are using this medicine.**

Patient interview

- **Hospital Name:**
- **Patient Name. :**
- **Age. :**
- **Gender. :**
- **Disease. :rheumatoid arthritis and osteoarthritis.**
- **Drug. : Diclofenac**
- **Drugs ADR**
- **feeling sick (nausea)**
- **being sick (vomiting) or diarrhea.**
- **feeling dizzy or vertigo.**
- **headaches.**
- **stomach ache, wind or loss of appetite.**

- **mild rash.**

- **Dosage frequency**

- **For acute pain:**
  - **Adults and children 12 years of age and older—25 milligrams (mg) 4 times a day.**
  - **Children younger than 12 years of age—Use and dose must be determined by your doctor.**

- **Route of administration**

- **Commonly used routes of diclofenac administration are as follows:**
  - **oral,**
  - **intramuscular, transdermal**
  - **intravenous, rectal**

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