Study of aceclofenac drug related with pharmacovigilance.

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Abstract

Aceclofenac is an oral non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory and analgesic properties. Although there are some differences in the authorized indications between countries, aceclofenac is mainly recommended for the treatment of inflammatory and painful processes, such as low back pain (LBP), scapulohumeral periarthritis, extra articular rheumatism, odontalgia, and osteoarthritis (OA), rheumatoid arthritis (RA), and ankylosing spondylitis (AS). The analgesic properties and tolerability profile of aceclofenac in musculoskeletal disorders are reviewed, focusing on relevant and recent studies. The efficacy and safety comparison of aceclofenac with other analgesics and anti-inflammatory agents in OA, AS, RA, and LBP is described. Relevant studies were identified following a literature search of PubMed using the terms ``aceclofenac" and "clinical trials" published from 1 Jan 1992 to 1 Jan 2020. Aceclofenac is at least as effective as other NSAIDs in reducing pain and/or improving functional capacity in chronic pain conditions (OA, AS, RA, and LBP). It is generally well tolerated and appears to have a more favorable GI profile than other NSAIDs. Thus, current evidence indicates that aceclofenac is a useful option for the management of pain and inflammation across a wide range of painful conditions.

Keywords: aceclofenac, NSAIDs, analgesia, osteoarthritis, low back pain pharmacovigilance,ADR,toxicology,

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Clinical Research
Definition
> Clinical trials are prospective biomedical or behavioural 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 paediatrics 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

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

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.

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.

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.

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)
>The identity 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 rights 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 use development experience several event that gave weight of greater harmonization within countries initially & then internationally in the U.S a terrible mistake in the formulation 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
>To provide an overview of the history of good clinical practice (ICH).
>To emphasize the importance of ICH GCP compliance when conducting clinical trials.
>To recognise the implications of non-compliance.
>To review positive & negative cause studies.
>Protect the patient.Avoid trials duplication (saving time money resource.
Scope of GCP
>Good clinical laboratories should be used by all laboratories where tests are done on biological specimen diagnosis patients 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 were 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 & caused & 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 drug.
>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 trials of drugs already approved for a certain claim initiated 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 ge-nder 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 institution.
>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 has 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 gap in understanding questions raised about issues needed to address CDSCO.
>How long post trials access medicine should provide to patients. This is of special importance because there is chronic disease with long treatment.
>How is safety signal monitored for this period? Would sponsor the 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 report.
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 hum

Concept of pharmacovigilance
Definition objective, types & components of pharmacovigilance

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 report voluntarily sent by health care professional for patient 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 defined period & actively followed up during treatment.

4. Targeted clinical investigation:

● These kinds of investigations are performed to identify the 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.

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● 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.
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4.
● 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
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 &
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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,   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, Kolkatta (Co-ordinator Dr. Anjan Adhikari)
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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, Tropical Medicine, Chittaranjan Avenue, Kolkata
(Co-ordinator -Dr. Santanu Tripathi)
7. Department of Pharmacology, JIPMER, Pondicherry (Co-ordinator -Dr. C Adithan)
School of
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)
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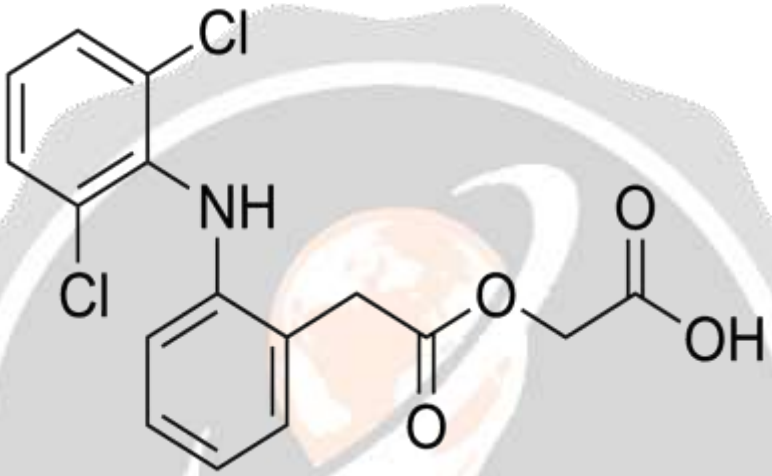
17.Department of Pharmacology, Santosh Medical University, Santosh Nagar, Ghaziabad
(Co-ordinator -Dr VC Chopra)
18. Department of Pharmacology, SMS Medical College , Jaipur (Co-ordinator -Dr. Mukul Mathur)
19.Department of Clinical Pharmacology, Christian Medical College,Vellore, Tamil Nadu
(Co-ordinator -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 professional about the importance to ADR reporting.
● To monitor the benefit risk profile of medicine.
● Generate independent, evidence based recommendation on the safety medicine.
● Support the CDSCO for formulation safety related regulatory decision 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
Druge name - Aceclofenac
Identification

>Aceclofenac is an oral non-steroidal anti-inflammatory drug (NSAID) with marked anti-inflammatory and analgesic properties used to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It is reported to have a higher anti-inflammatory action or at least comparable effects than conventional NSAIDs in double-blind studies 2,3,5. Aceclofenac potently inhibits the cyclo-oxygenase enzyme (COX) that is involved in the synthesis of prostaglandins, which are inflammatory mediators that cause pain, swelling, inflammation, and fever. Aceclofenac belongs to BCS Class II as it possesses poor aqueous solubility

Structure :



Chemical formula :

C16H13Cl2NO4

Synonyms:
> Aceclofenac
>Aceclofenac
> betadex
>Aceclofenac
>Aceclofenaco

Discovery and development:
>Typically researchers discover new drugs.
>New insight into a diseases process that allow researches to design a product to stop or reverse the effect of the disease.
>Many test of molecular compounds are possible. Beneficial effects against any of a large number of disease.New technology such as these that provide new way's to target medical products to specific fitness in the body or to generic material.

Development:
>Once researchers identify promising compound observed and distributed. It is potential benefits and mechanism of action. The best dosage .side effects or adverse events that can often be referred to as toxicity. How it interacts with other drugs and treatment. The best interacts with other drug and treatment. The best way to give the drug.

Pre clinical research :
>Before testing a drug in people, researchers must find out whether it has the potential to cause harm, also called toxicity.
Two types of pre clinical research
1)In vivo
2)In vitro
1)In vitro
>Cell lines are derived from either human or non animal and are
introduce how pharmaceuticals are under development within a ref dish or cost tube . In vitro studies have many benefits was abhivour benefits is that they do not cause harm to the animal or person that the cell cultures have been derived from.
2)In vivo
>In vivo studies in compression to in vitro take place with on living organism. In preclinical trial in these happens with in animal subject. In clinical trial in vivo studies can use either human animal are subjected. In vivo studies are also undergoing a technological transformation.

These generation set the also minimum basic requirements for
- Study conduct
- Equipment
- Written protocols
- Study report
- A system of quality assurance

Clinical research:
>Phase -01
Completed treatment purpose anticellular agent or healthy subject.
Active not other bioequivalence secruting.
>Phase 02
Completed prevention purpose symptomatic reversible
>Phase 03
Completed treatments purpose disorder of urinary stent.
>Phase 04
Completed treatment purpose osteoarthritis of the knee or osteoarthritis and
NSAID associated with gastroduodenal injury .
Pharmacokinetics <ADME >
● Absorption
>Aceclofenac is rapidly and completely absorbed from the gastrointestinal tract and circulates mainly as unchanged drug following oral administration. Peak plasma concentrations are reached around 1.25 to 3 hours post-ingestion, and the drug penetrates into the synovial fluid where the concentration may reach up to 60% of that
in the plasma 11. There is no accumulation in regular dosing, with similar maximum plasma concentration (Cmax) and time to reach peak plasma concentration (Tmax) after single and multiple doses .

● Volume of distribution
>Aceclofenac penetral in to the synovial fluid where tbe concentration rech
approximately 57% of those in plasma . the volume of distribution is approximately 25l . the mean plasma elimination half life is around 4 hours.

● Metabolism
>hydroxy aceclofenac is the main metabolite detected in plasma however other minor metabolites include diclofenac, 5-hydroxy aceclofenac, 5-hydroxydiclofenac, and 4'-hydroxydiclofenac 2. It is probable that the metabolism of aceclofenac is mediated.

● Route of elimination
>The main route of elimination is via the urine where the elimination accounts for 70-80% of clearance of the drug 2. Approximately two thirds of the administered dose is excreted via the urine, mainly as glucuronidated and hydroxylated forms of aceclofenac 11. About 20% of the dose is excreted into feces 6.

Toxicity :
>Some common adverse effects include gastro-intestinal disorders (dyspepsia, abdominal pain, nausea), rash, ruber, urticaria, symptoms of enuresis, headache, dizziness, and drowsiness 12. Oral LD50 value in rats is 130 mg/kg.
Pharmacodynamics :
>Aceclofenac is a NSAID that inhibits both isoforms of COX enzyme, a key enzyme involved in the inflammatory cascade. COX-1 enzyme is a constitutive enzyme involved in prostacyclin production and protective functions of gastric mucosa whereas COX-2 is an inducible enzyme involved in the production of inflammatory mediators in response to inflammatory stimuli. Aceclofenac displays more selectivity towards COX-2 (IC50 of 0.77uM) than COX-1 (IC50 of >100uM), which promotes its gastric tolerance compared to other NSAIDs. The primary metabolite,4'-hydroxy aceclofenac, also minimally inhibits COX-2 with IC50 value of 36uM 2. Although the mode of action of aceclofenac is thought to mainly arise from the inhibition of synthesis of prostaglandins (PGE2), aceclofenac also inhibits the production of inflammatory cytokines, interleukins (IL-1β, IL-6), and tumor necrosis factors (TNF) 1,2. It is also reported that aceclofenac also affects the cell adhesion molecules from neutrophils 8. Aceclofenac also targets the synthesis of glycosaminoglycan and mediates chondroprotective effects.

Mechanism of action :
>Through COX-2 inhibition, aceclofenac downregulates the production of various inflammatory mediators including prostaglandin E2 (PGE2), IL-1β, and TNF from the arachidonic acid (AA) pathway. Inhibition of IL-6 is thought to be mediated by diclofenac converted from aceclofenac 6. Suppressed action of inflammatory cytokines decreases the production of reactive oxygen species. Aceclofenac is shown to decrease production of nitrous oxide in human articular chondrocytes 2. In addition, aceclofenac interferes with neutrophil adhesion to endothelium by decreasing the expression of L-selectin (CD62L), which is a cell adhesion molecule expressed on lymphocytes 8. Aceclofenac is proposed to stimulate the synthesis of glycosaminoglycan in human osteoarthritic cartilage which may be mediated through its inhibitory action on IL-1 production and activity 1. The chondroprotective effects are generated by 4'-hydroxy aceclofenac which suppresses IL-1 mediated production of promatrix metalloproteinase-1 and metalloproteinase-3 and interferes with the release of proteoglycan from chondrocytes

Indication:
>Aceclofenac is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.
Drug interaction :
>Acebutolol: Aceclofenac may decrease the activities acebutolol.
>Amlodipine: Aceclofenac is may decrease the antihypertensive activities of

>Amlodipine.Atenolol: Aceclofenac may decrease the antihypertensive activities of atenolol. Betaxolol Aceclofenac may decrease the antihypertensive activities of betaxolol.
Food interaction:
>Take with or without Food.
Side effects:
>Nausea
>Vomiting Diarrhea Flatulence Constipation Dyspepsia
>Abdominal pain

International Brand Name :
>Cinco De Lanza Hifenac
Uses
>Relief of pain and inflammation in osteoarthritis rheumatoid arthritis and ankylosing spondylitis

Availability:
>The generic Aceclofenac is manufactured by one company
medindias drug directory has currently 340 brands of aceclofenac listed. New generics and brands are constantly seing updated and they are approved by the drug controller and available in the pharmacy's hospital.

Dose of paracetamol Aceclofenac:
>Paracetamol is a component of Aceclofenac paracetamol which can cause liver injury when in large doses.

Aceclofenac Tablets:
>Zerodol
>sp Aceclo
> sp Pyrac sp

Selling of Aceclofenac Drug :
>Aceclofenac market size was usp million and it is possible to reach us by
the end of 2027 with 2021 2027. By application osteoarthritis musculoskeletal pain systematic traumatic pain ankylosing spondylitis rheumatoid arthritis chronic infection arthritis other by types tablet capsule region and forecast to 2027 . the Aceclofenac market report contains a full toc tablet and figures chart with in depth analysis.
We have been tracking the direct impact of covid 19 on this market as well as
the indirect impact from other industries. This report analyzes the impact of the pandemic on the Aceclofenac market from a global and regional perspective.

Aceclofenac market report are :
Navipharm
Sk chemical Hanmi
Glenmark pharmaceutical Bausch health
Daewoong
Bayer
Bms
Ucb
Sichuan weigo pharmaceutical
The drug marked as Aceclofenac Tablet .Aceclofenac was upload developed as an analog to diclofenac to produce a drug. First approved 1992 it has since then become more popular to it is in europe.

Identification of most widely prescribed drug from selected class consumption report by approaching pharmacy stores company representatives and pharma companies web portals:

>Overall 78% of patients regularly consumed of 11,340 patients were studied.
Mean age 75.1+7Years female 61.5% two percent of patients were.
Nationalized and were older or =1.2 predominantly female or 1.3 had more co
morbidity or 3.5 p<0.001 and lower geriatric scale scores. Institutionalized patients consumption of paracetamol tramadol and Aceclofenac was higher 54.3%19 %and 7.6 %respectively

Aceclofenac Tablets uses :
>Aceclofenac tablet belong to a group of medicine called
non steroidal anti inflammatory drug .NSAIDS They have anti inflammatory and painkiller properties causing a lowering of swelling redness inflammation and pain. The medicine active ingredient Aceclofenac Tablet is aceclofenac.

Do not take Aceclofenac tablet :
>If you're allergic to Aceclofenac or any of the ingredients of this medicine. If you are allergic to aspirin or any other NSAIDs such as ibuprofen naproxen or diclofenac.if you have taken aspirin or any the NSAIDS and experienced one of the following. Asthma attack causing tightness in the chest wheezing and difficulty breathing.

Warning and precautions :
>Before you start taking Aceclofenac tablets, tell your doctor.
>If you suffer from any form of kidney or liver disease.
>If you have or have ever had problems with the circulation of blood . Asthana and breathing problems.
>If you Smoke
>If you diabetes
>Aceclofenac Tablets must be taken preferably with or after food.

How to take Aceclofenac Tablet :
>Always take this medicine exactly as your doctor or pharmacist has told you. You will be prescribed the lowest effective dose over the shortest duration to reduce side effects.
Check with your pharmacist if you are not sure. The recommended dose in adults is 200mg a day. One 100mg tablet should be taken in the morning and o e the evening.

Children:
>Aceclofenac tablets are not recommended for use in children under the age of 18.Do no or chew the table .Do not exceed the stated daily Dose.

Elderly:
>If you are elderly you are more likely to experience serious side effects. You will be given the lowest effective dose over the shortest duration of treatment.

Reporting Of Side Effects:
If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effect directly not listed in this leaflet. You can also report side effects directly vid the yellow card scheme at WWW.MHARA.GOV.UK YELLOW CARD.

How Take Store Aceclofenac Tablet:
Keep this medicine out of the sight and reach children. Do not use this medicine after the expiry date which is stated o. The cartoon after Exp the expiry date refers to the last day of that month.
Stored below in 25°c.
Do not throwaway any medicine vid water or household throw away medicine you no

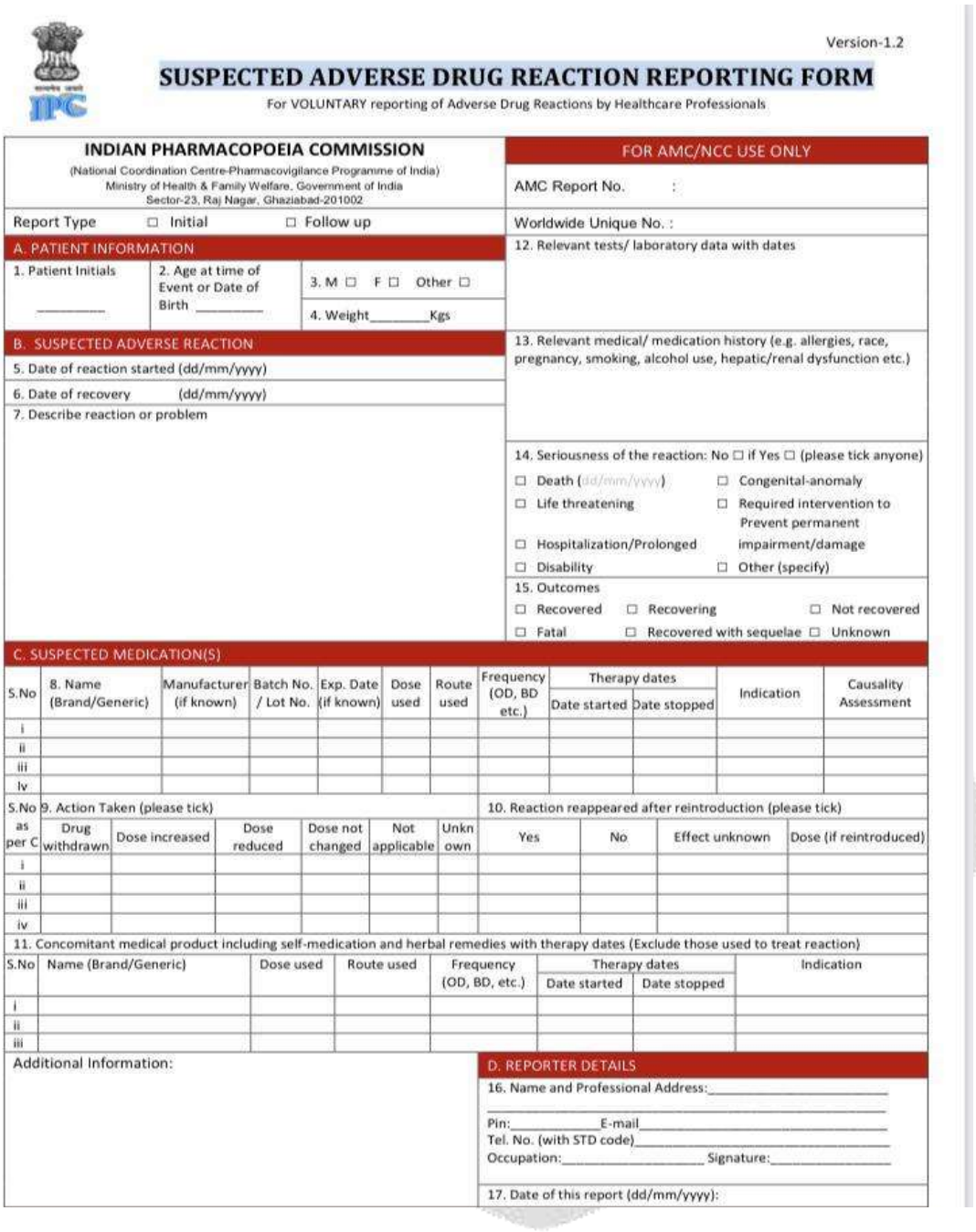
Identification of adverse effected of selected drug :
>Aceclofenac :
>Generic name:Aceclofenac
>Brand Name: cinco feb
Clanza Cr
Hifenac
>Drug class : Non steroidal anti inflammatory drug

What are side effect of clanza cr
>gastrointestinal disorder indigestion heartburn abdominal pain nausea
>rash
>redness
>hives
>headache
>dizziness
Side effect:
>The majority of side effects observed have been reversible and of a minor nature and include gastrointestinal disorder (dyspepsia,abdominal pain ,nausea,rash,rubber,urticaria,symptoms of enuresis, headache , dizziness and drowsiness.

Precaution:
>Use in pregnancy and nursing mothers since there is no information on the safe use of clanza cr during pregnancy and location the use of clanza or should therefore be avoided in pregnancy and location

Use in children:
>The dosage & indication is not established yet for children under 6 years old

Adverse Drug Reaction (ADR) Monitoring Form
Preparation of ADR monitoring form as per guidelines given by AMCs
(e.g. IndianPharmacopoeiaCommission)



Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION
(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

FOR AMC/NCC USE ONLY
AMC Report No. :
Worldwide Unique No. :

Report Type ☐ Initial ☐ Follow up

A. PATIENT INFORMATION
1. Patient Initials _____
2. Age at time of Event or Date of Birth _____
3. M ☐ F ☐ Other ☐
4. Weight_____Kgs

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION
5. Date of reaction started (dd/mm/yyyy)
6. Date of recovery (dd/mm/yyyy)
7. Describe reaction or problem

13. Relevant 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 impairment/damage
☐ Hospitalization/Prolonged
☐ 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. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates		Indication	Causality Assessment
								Date started	Date stopped		
i											
ii											
iii											
iv											

S.No as per C	9. Action Taken (please tick)						10. Reaction reappeared after reintroduction (please tick)			
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unkn own	Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates		Indication
					Date started	Date stopped	
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS
16. Name and Professional Address:_____
_____
Pin:_____E-mail_____
Tel. No. (with STD code)_____
Occupation:_____ Signature:_____

17. Date of this report (dd/mm/yyyy):

Hospital visit
> Side effect :
Nausea
vomiting
diarrhoea
flatulence
constipation
dyspepsia
abdominal pain

melaena, haematemesis
ulcerative stomatitis

>Serious side effects:
Long term use may lead to serious complications such as stomach bleeding and kidney problems.
It may cause dizziness, drowsiness or visual disturbances. Use caution while driving or doing anything that requires concentration.

>Serious allergic reaction:
Skin. Aceclofenac cream can cause erythema, itching, and a burning sensation in under 3% of patients [SEDA-20, 91]. Aceclofenac can cause photosensitivity.

Patient interview

Hospital Name:

Patient Name. :

Age. :

Gender. :

Disease. :.relief of pain and inflammation in osteoarthritis rheumatoid rheumatoid arthritis & ankylosing spondylitis.
Drug. : Aceclofenac

>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

Reference

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- http://www.pharmabiz.com/PrintArticle.aspx?aid=63422si
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- https://www.pipelinepharma.com/marketplace/diclofenac-manufacturers
- https://scholar.google.co.in/scholar?q=key+findings+of+diclofenac&hl=en&as_sdt=0&as_vis=1&oi=scholart
- https://clincalc.com/DrugStats/
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- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097540/#:~:text=Commonly%20used%20routes%20of%.