Review -Pharmacovigilance – adverse drug reactions, clinical trials and benefits of Naproxen

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Abstract :

Pharmacovigillance defined by the world health organization as the"science & activities relating to the detection, assessment, understanding,& prevention of adverse effects or any other drug related problem. "pharmacovigilance plays a key role in ensuring that patients receive safe drugs.our knowledge of drugs adverse reactions can be increased by various means,including spontaneous reporting,intensive monitoring & database studies.New process both at a regulatory & scientific level are developed with the aim of strengthning Pharmacovigillance.

Here's it includes safety,efficacy,clinical,preclinical trials,health benefits and side effects of Naproxen as well as which conditions it may treat Naproxen is a nonsteroidal anti – inflammatory drug (NSAIDs) advocate for use in painful and inflammatory. Nonsteroidal anti- inflammatory drug NSAIDs are the main therapeutic alternative in treating pain and inflammation among various population.

Keywords – Pharmacovigilance ,clinical and non-clinical trials, naproxen drug,adverse effect

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Introduction : 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.

- Clinical Research :

- Definition : clinical trials is a prospective ethically designed investigation in human subjects to objectively discover /varify / compare the result of two or more therapeutic measures (drug) .
- Classification : 1) pre-clinical trials

  2) clinical trials

- Pre-clinical trials : After synthesizing / identifying a prospective compound it is tested on animal to expose the whole pharmacoeidemiological profile experiment are generally perform on a rodent (mause , rate guinea pig) rabbit etc then on a larger animal (cat ,dog , monkey) .
- Steps are performed

1) Screening test : These are simple and tapidly performed test indicate presences or absence of particular pharmacodynamic activity that a sought .for e.g – analgesic or hypoglycemic activity .
2) Test on isilated organ bacterial cultures etc : Theses also are preliminary test to detect specific activity such as antihistaminic anti secretary vasodilator anti bacterial etc
Bacteria are one-celled organisms. There are many different kinds of bacteria. They live just about everywhere in your body and on your skin. Some types of bacteria are harmless or even helpful. Others can cause infections and disease.

A bacteria culture test can help find harmful bacteria in or on your body that may be making you sick. To do the test, you will need to give a sample of your blood, urine, skin, or other tissue. The type of sample depends on where the infection seems to be located.

To find out what type of bacteria you may have, a health care professional will need to examine a large number of bacteria cells. So, your sample will be sent to a lab where the bacteria cells will be grown until there are enough for the test. Test results are often ready within a few days. But some types of bacteria grow slowly, so sometimes your results may take several days or longer.

3) Test on animal models of human disease : such as kindled seizures in rat spontaneously genetically hypertensive rats experimental tuberculosis in mouse alloxan induced diabetes in rat or dog etc . Animal models of human disease are commonly utilized to gain insight into the potential efficacy and mode of action of novel pharmaceuticals. However, conventional (healthy) rodent and nonrodent models are generally utilized in nonclinical safety testing. Animal models of human disease may be helpful in understanding safety risks of compounds in nonclinical or clinical development, with their greatest value being in targeted or hypothesis-driven studies to help understand the mechanism of a particular toxicity. Limitations of animal models of disease in nonclinical safety testing include a lack of historical control, heterogeneity in disease expression, a limited life span, and confounding effects of the disease. In most instances, animal models of human disease should not be utilized to supplant testing in conventional animal models. While of potential benefit, testing in an animal model of human disease should only be taken after adequate consideration of relevance along with benefits and limitations of the proposed model.
4) Confirmatory tests and analogous activities : Compounds found active are taken up for detailed study by more elaborate (Complex) tests which confirm and characterize the activity. Other related activities also measured, like antipyretic and anti-inflammatory activity in an analgesic. 6. Mechanism of action: Attempts are made to find out the mechanism of action. E.g. whether an anti-hypertensive is an α blocker/β blocker/ ACE inhibitor/ calcium channel blocker, etc.

5) Systemic pharmacoeidemiology : Irrespective of the primary action of the drug it's effects as major organ systems such as nervous cardiovascular respiratory renal GIT are worked out mechanism of action including additional mechanism.eg – alpha -adrenergic , blockade , calcium channel blockade etc .beta – adergenic blocker anti hypertensive
6) Quantitative tests : The dose response relationship maximal effect of comparative potency efficacy with existing drugs is oscretained .
7) Pharmacokinetics : The absorption volume of distribution metabolism excretion patterns of tissue distribution and plasma half life of the drug .
8) Toxicity test : The aim is to determine safety of the compound in at least 2 animal spacies one rotent and one rodent .eg – mouse / rat and dog by oral and parentral route .

- Types : 1) Acute toxicity : single dose are given to small groups of animal that are observed for over effect of mortility for 1-3 days .The dose which kill's 50 % animals (LD50) is calculated. Organ toxicity is examined by histopathology an all animals .

2)Sub- acute toxicity : Repeated dose are given for 2-12 week's depending on the

Duration of intended treatment in man .dose are selected on the basis of ED50 and LD 50.

Animal are over effect food intake body weight hematology etc and organ toxicity . 3) Chronic toxicity : The drug is given for 6- 12 months and effect are studied in a subacute toxicity. This is a generally undertaken with clinical trials .

4) Reproduction and teretogenesity : The effects of spermatogenesis ovulation fertility and developing foetus are studied.

5) Mutagenecity : Ability of drug to induce the genetic damage in bacteria mamation cell ahd intact rodents .

6) Carcinogenicity : This genisty is standardised procedure under good laboratory practice GLP the conduct of animal experimental and toxicity testing .

- Clinical trials : where a compound reserving trial in man is identified animal studies the regulating authorities are approached who an satisfaction tissue an the investigation new drug IND license. Standard for design ethics conduct monitoring ouditing recording and analyzing data reporting of clinical practice GCP guidelines by an International Conference of Hormonization ICH. National agencies in most countries including ICMR (indian council of medical research) in india it is also formed by ethical guideline for by clinical trials .
- The clinical studies are divided into four phases :

- Phase 0 : microdosing study : Phase 0 of a clinical trial is done with a very small number of people, usually fewer than 15 . Investigators use a very small dose of medication to make sure it isn't harmful to humans before they start using it in higher doses for later phases. If the medication acts differently than expected, the investigators will likely to do some additional preclinical research before deciding whether to continue the trial.

  Phase I-Human pharmacology and safety : During phase I of a clinical trial, investigators spend several months looking at the effects of the medication on about 20 to 80 people who have no underlying health conditions.This phase aims to figure out the highest dose humans can take without serious side effects. Investigators monitor participants very closely to see how their bodies react to the medication during this phase.While preclinical research usually provides some general information about dosing, the effects of a medication on the human body can be unpredictable.

- Phase II – Therapeutic exploration and dose ranging : Phase II of a clinical trial involves several hundred participants who are living with the condition that the new medication is meant to treat. They're usually given the same dose that was found to be safe in the previous phase. Investigators monitor participants for several months or years to see how effective the medication is and to gather more information about any side effects it might cause .While phase II involves more participants than earlier phases, it's still not large enough to demonstrate the overall safety of a medication. However, the data collected during this phase helps investigators come up with methods for conducting phase III.

  Phase III – Therapeutic confirmation comparison : Phase III of a clinical trial usually involves up to 3,000 participants who have the condition that the new medication is meant to treat. Trials in this phase can last for several years.The purpose of phase III is to evaluate how the new medication works in comparison to existing medications for the same condition. To move forward with the trial, investigators need to demonstrate that the medication is at least as safe and effective as existing treatment options.To do this, investigators use a process called randomization. This involves randomly choosing some participants to receive the new medication and others to receive an existing medication.Phase III trials are usually doubleblind, which means that neither the participant nor the investigator knows which medication the participant is taking. This helps to eliminate bias when interpreting results.The FDA usually requires a phase III clinical trial before approving a new medication. Due to the larger number of participants and longer duration or phase III, rare and long-term side effects are more likely to show up during this phase.If investigators

demonstrate that the medication is at least as safe and effective as others already on the market, the FDA will usually approve the medication.

- Phase IV – postmarketing surveillance data gathering studies : The drug has been marketed for general use practicing physician are identified about the efficiency acceptability and adver. Further therapeutic trials dike children pregnant women patient with hepatic diseases etc .most drugs continue their development parents even after making .

- Function of drug controller general of India (DCGI) :

DCGI is a responsible for approval of new drug medical device and clinical trials to be conducted in india .

He is appointed by the central government under the DCGI the state drug control organisation will be functioning .

The DCGI is a advised by the drug technical advisory board (DTAB) and drug consultative committee.

Drug controller general of India is responsible for approval of license of specific categories of drug such as blood and blood products IV fluids vaccine and sera .

- Central drugs standard control organisation (CDSCO) :

1) Approval of new drugs and clinical trials.

2) Import registration and licensing .

3) Testing of new drug .

4) Grant of test license personal license 100 cs for export .

5) Baning of drug and cosmetics

6) Licence approving of vaccines rDNA products.

- Type of regulatory application :

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

Preclinical testing : consists of animal pharmacology and toxicology studies to assess whether the drug is safe for testing in humans .

Manufacturing information : includes composition manufacture and stability of the controls used for manufacturing the drugs.

Clinical trials protocols : The protocols for proposed clinical studies to initial phase trials will expose the subject to unnecessary risk .

- New drug application (NDA)

1) An application submitted by the manufacturer of a drug to the FDA after clinical trials have been completed for a licence to the market the drug for specific .

2) New drug application NDA vehicle in the United State through which drug sponsors normally propose FDA appea new .

3) The dates garnered the during me animal studies and human clinical of an investigated and new drug IND become part of NDA .

- Abbreviated new drug application (ANDA) :

1) An application of license to market generic or duplicate version of drug that has already been granted an app rovel under a full NDA

2) Drug has already met the Saturday standard for safety and effectiveness.

3) A genetic drug product is one that is comparable in dosage form strength route of administration quality performance characteristics intended use .

- Good clinical practice :

- Objective and scope of ICH Good Clinical Practice :

Protect the patient to provide a untiled standard for the European union EU japan and United States to facilate mutual acceptance of clinical data by the authorities in these jusdiations .
Facilate the mutual acceptance of clinical across ICH GCP region .

Avoid trials duplication (saving time money) .

Facilate global submission through mutual acceptance of data .

Technical requirements for medicinal products containing new .

To provide an overnew of the history of good clinical practice international conference on Harmonizations .
To emphasize the importance of ICH GCP compliance when conducting clinical

trials .

To understanding the roles and responsibility of the parties involved including investigators sponsor and committee.
To discuss key aspects of GCP such as pateint requirements consent and dada privacy .
To recognise the implications of non compliance .

To review positive and negative case studies .

- Scope :

  Good clinical practice GCP : A standard for the design conduct performance monitoring auditing , recording ,analyse and reporting results are credible and accurate and that the right integrity and confidentiality of trial subject are protected .
  The objective of this guidelines is to outline the mission and the organisation of a sponsor auditing department and the principal for planning performance and reporting audits all of which should be considered when the auditor who to the sponior performs an audita clinical trials performed by the sponsor . This guidelines is expected to be a basic principles along with international conference on Harmonizations ICH Good Clinical Practice GCP for a sponsor auditor to conduct on audit in the various situations of each country and sponsors .

- New drug and clinical trials rules 2019 :

  This document summarizes major changes affecting ethics committee (EC) after coming into force of the New Drugs and Clinical Trials Rules 2019 (New rules), i.e. GSR
  227 (E) by India's Ministry of Health and Family Welfare (MoHFW).

  EC means, for the purpose of:

  i. Clinical trial (CT), EC, constituted under Rule 7 and registered under Rule 8 of the New CT rules ii. Biomedical and health research, EC, constituted under Rule 16 and registered under Rule 17 of the New CT rules.

  A clinical trials is a systemic study of new drug or investigational new drug in human subjects to generate data to determine the safety efficacy or toxicity of a new drug or investigational new drug in a view to dicover new molecule .

  For a new molecule to be commercilative in has to undergo various rigorous phases of preclinical and clinical studies .

  In general it takes about 10- 20 years of intense study on the new molecule before the release of the drug into the market .

  Clinical studies involve the research to estimate the safety and efficacy of the drug in humana .

  It is a necessary to take their conditions consent before subjecting the group of people (participants in clinical studies) .

  However the safety of the participants being a major concern the sponsers and the investigators must follow ethical principle and must implement good clinical practice .

- Protocol designing for clinical trials : Every clinical investigation begins with the development of a clinical protocol. The protocol is a document that describes how a clinical trial will be conducted (the objective(s), design, methodology, statistical considerations and organization of a clinical trial,) and ensures the safety of the trial subjects and integrity of the data collected.describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project. According to the ICH Good Clinical Practice guidelines, a protocol should include the following topics .
- Title Page (General Information)
- Background Information

- Objectives/Purpose
- Study Design
- Selection and Exclusion of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Adverse Events
- Discontinuation of the Study
- Statistics
- Quality Control and Assurance
- Ethics
- Data handling and Recordkeeping
- Publication Policy
- Project Timetable/Flowchart
- References
- Supplements/Appendices

- Concept of pharmacovigilance :
- Definition, objective, types, and components of pharmacovigilance :
- Definition of pharmacovigilance : Pharmacovigilance means the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems .
- Objective :
- To create a nation-wide system for patient safety reporting .
- To identify and analyze the new signal (ADR) from the reported cases .
- To analyses the benefit - risk ratio of marketed medications .
- To generate the evidence based information on safety of medicines.
- To support regulatory agencies in the decisionmaking process on use of medications .
- To communicate the safety information on use of medicines to various stakeholders to minimize the risk .
- To emerge as a national center of excellence for pharmacovigilance activities .
- To collaborate with other national centers for the exchange of information and data management .

- Types :
- Passive surveillance

- Active surveillance
- Cohort event monitoring • Targeted Clinical Investigations
- Passive surveillance :

Passive surveillance methods involve the usage of spontaneous adverse event reports voluntarily sent by healthcare professionals or patients to the marketing authorization holder or regulatory authority. Here, data related to the adverse reactions are collected in a central or regional database. The identity of the reporter

remains anonymous, but patient-related details like country, age, gender, and preexisting co-morbidities can be recovered from the reporting forms .

Example :

FAERS (FDA Adverse Event Reporting System) database run by FDA.

VigiBase™, the WHO Global Individual Case Safety Report (ICSR) database. For Europe:EudraVigilance maintained by European Medicines Agency.

- Active surveillance : This method aims to monitor certain specific drug-related adverse events and seeks to ascertain the number of adverse drug reactions entirely through a pre-planned process. It is commonly known as toxicity monitoring or safety monitoring.
- Cohort event monitoring : In this method, the surveillance study is planned prior to beginning the treatment with the medication. A group of people are exposed to a r
- drug for a defined period and actively followed up during treatment.

Adverse events of the target drug or the events associated with one or more

medicines taken with that drug are monitored.

- Targeted Clinical Investigations

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 disorders, pregnant women, and older people.

- Components :

Adverse Event Case Management including expedited reporting

Aggregate Reporting

Signal Intelligence

Risk Management.

1) Adverse event case management including expedited reporting : An adverse event is any upward medical occurance in a patient administerd a medical product and which dose not nessarly have to have a causeal relationship with this treatment .An adverse event can there fore be any unfavorable and unintended sign e.g (an abnormal laboratory findings) symptoms or disease temporally associated with the used of a medical product or not considered related to the medical product .
2) Aggregate Reporting : Aggregate Reporting refer to those reports that focus not so much on individual cases but rather an overview assessment of the safety profile and benefits risk evaluation .
   e.g : 1) periodic safety updated repots (PSUR) periodic benefit risk evaluation reports (PNRERs) : It is pv documents intended to provide an evaluation of risk benefits batance of

medical product for submission by markating authorisation holder by defined time points during the post authorisation phase o Source of safety information. o Active surveillance system .

- Clinical data trials. o Competen authorities updates and website. o Publication . o Non clinical studies update .
- Post authorisation use in special populations.

- Table of content PSUR

1) International

2) Worldwide marke authorisation status 3) Action takes in the reporting interval for reason .

4) Changes to reference safety information .

5) Data in summary tabulation.

6) Summories of significant findings from clinical trials during the reporting interval.

7) Finding from non – interventional.

8) Info from other source .

9) Non – clinical data.

10) Literature

11) Other periodic reports .

12) Signal and risk evaluation.

13) Benefit evaluation .

14) Conclusion and actions .

15) Appendices to PSUR.

- Periodic benefit risk evaluation PNRERs :

Reson of AE reports

Protection of human subjects

Collection of clean and reproducible data

Regulatory perspective

Analyze data and determine risk benefits

Before giving permission to markate

AE can be

Any unfavorable and unintended sign

Including and abnormal lab finding

Symptoms

Disease

- Development safety updated research (DSUR) :

  This are new internationally harmanian safety documents covering the summary of medicinal products during there development or clinical trials phase .they are based heavily on the PSUR format alredy used for updating the trilogy is well placed to support our clients in all elements of DSUR and other safety documents development
- Integrated summaries of safety :

  A integrated summary of the safety profile from all clinical studies (include phase I)

  Summary of animal data important to human safety

  Drug – Drug demographic and drug disease interaction

  The extent of exposure the no of patient exposed and no exposed to various dose for define duration .
- Clinical summarise safety : A summarise of clinical safety (SCS) contains a summary of data retevant to safety in the intended patient population integating the result of individual .
- Signal intelligence : pv signal intelligence practice are focused on adopting DPA algorithm to mine SRs data for constituting hypothese of signal drug to the establish evidence based medicine to confirm or refulte causality association between those pairs .Then regulatory actions may be action may be taken to protect the public health .
- Risk management : Risk management in pharmacovigilance is undertaken to promote safe used of medicines and safeguard health of patient it is active set performed for identification of risk management has following stage.
  1) Identification and characterization of the safety profile of the medical products .
  2) Planning or pv activities to characteristics risk and identify new risk
  3) Planning and implementation of risk minimization and mitigation and assessment of the effective of theses activities .
  4) Documents post approval obligation that have been imposed as a condition of marketing Authorize .
- Constitutional and objectives of pharmacovigilance program of India :
- Objective : To monitor adverse drug reactions (ADRs) in india population

  To create acuazness amongst health care professional about the importance of

  ADR reporting of India

  To moniter benefits risk profile of medicin

  To create a national wide for patient safety reporting

  To identify and analyzing new signal from the report cases

Generate independent evidence based recommendation on the safety of medicines
Support the CDSCO for formulating safety related regulatory decision for medicines
Community finding with all key shakeholders

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

- Constitution :

Pharmacovigilance mainly involved monitoring and reporting of adverse drug reactions assosiated with the use of medicinal products .Under reporting of advers drug reaction is a seriouse issue hampering the dynamic of pharmacovigilance programme .pharmacovigilance of all shake holder .

- ADR monitoring centres (AMC) :

1) Department of pharmacology Enbs therapeutic and toxicology government medical , college,Bakshi nagar jammu .
2) Department of pharmacology PGIMER

3) Department of pharmacology R.G medical College Kolkata

4) Department of pharmacology lady hardinge medical college new delhi .

5) Department of pharmacology jipmer pondicherry

6) Department of pharmacology Jss medical college hospital Karnataka 7) Department of clinical pharmacology Christian medical college Vellore terminate .
8) Department of pharmacology Guwahati asam .

9) Institute of pharmacology Madras medical College jaipur .

10) Department of pharmacology santosh nagar medical university Gazibad .

Function :

1) To optimism safe and effective use of medicines in set up.

2) To create awareness amongst health care professional about the importance of ADR reporting.
3) To monitor benefits risk profile of medicine.

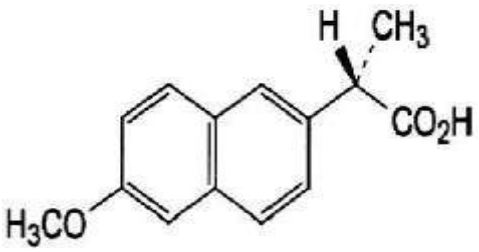
4) Generate independent evidence based recommendation on the safety of medicines.
5) Collection of ADR reports .

6) Perform follow up with the complainant to check complete ness as per sop's 7) Data entry into virgiflow .

International conference on Harmonization on ICH E2e Guideline

Drug : Naproxen

Generic name : naproxen [na-pox-en] Brand name :
Aleve , Ec-Naprosyn , flanax pain Structure :



Molecular Formula *:* C14H14O3

Molecular weight : 230.26 g/mol

IUPAC Name *:* [d-2(6-metoxy-2 naphtyl) propionic acid]

Drug class : Nonsteroidal Anti-Inflammatory Drug (NSAIDs)

Synonyms : propionic acid
Density : 1.35 g/cm3

Uses :

- Naproxen is used to relieve pain from various conditions such as headache .
- Muscle aches tendonitis dental pain and menstrual cramps .
- It also reduces pain swelling and joint stiffness caused by arthritis bursitis and gout attack .
- Introduction : Naproxen was initially approved in 1976 for prescription use and remained a prescription drug until it received approval as an over-the-counter (OTC) medication in 1994.Naproxen is a nonsteroidal anti inflammatory drug (NSAID) it is works by reducing hormones that cause inflammation and pain in the body .Naproxen is used to treat pain or inflammation caused by conditions such as arthritis, ankylosing , spondylitis , tendonitis , bursitis, gout or menstrual cramps. It can also be used to treat acute pain caused by other conditions not listed in this medication guide. Indisputable nonsteroidal anti inflammatory drug NSAID prevail in the prescribed therapeutic approaches constituting approximately 80 % of all prescription . similar data can be substantiated by key role of those drug is pain and inflammation control symptoms defined yet in ancient time by the Greek philosopher Epicurus as the greatest evil facing humanity at same time the drug outlined as deliverance from febrile conditions pain syndrome and rheumatologic complaints are found to be among the leading causes for hospitalization following adverse drug reaction. The positive benefit / risk ratio for naproxen has been confirmed also by comprehensive observational surveys and meta analysis of data supplied by real clinical practice .The evidence for antipyretic anti inflammatory and analgesic effect a naproxen has been accumulated after the impressive nearly 45 year real clinical experience non steroidal anti – inflammatory drug is a class of analgesic medication that reduces pain ,fever and inflammation .
  Pain – It is Neurophysiological sensation arising from noxious stimulus .

  Inflammation - It is a localized physical condition in which part of the body becomes reddened , swollen, hot and often pain full especially as a reaction to infection . Fever – It is a elevation of body temperature it is inflammation is the immediate of our body in response of harmful stimulus .
  Reduction of inflammation with NSAIDs often results in relief of pain significant periods .
- Safety monitoring during clinical trials :
- Development : Naproxen was first released to the prescription drug market in 1976 under the name naproxen . In 1980 it's counterpart salt naproxen sodium was released for prescription use only under the name anaprox . In June of 1994, the FDA approved naproxen's use for an over-the-counter drug in low doses, this new drug was advertised as Aleve and marketed by Bayer HealthCare .
- Discovery : Naproxen is a naphthalene propionic acid derivative that is widely sold as its sodium salt. It is a nonsteroidal anti-inflammatory drug that is used to reduce pain, fever, and inflammation in muscles and joints. Its preparation in racemic form was first reported in 1968 in a patent awarded to Syntax.
- Preclinical Research :
- Pharmacodynamics :
- The mode of action of the active substance underlying the desired effect(s) should be described. The way the active substance affects body organs and organ systems should be described in relation to dose and desired therapeutic effect, as well as secondary and adverse effects.
- Pharmacodynamic (PD) studies may include e.g. in vitro, in vivo and ex vivo designs.

- Regardless of the experimental design employed and the method(s) of measurement, the NSAID effect should be fully described and justified by the applicant .
- Experimental models should be fully valid for their intended purpose. For example, in an in vivo model the suitability of parameters such as the choice of response variables, assessment time points and observation intervals should be established in relation to the expected and clinically relevant level and duration of effects. If the IVMP produces a long-acting effect, it is important to choose an experimental model with a sufficiently long duration to obtain a reliable result.
- In in vivo studies NSAID effects may be measured directly (e.g. reduction of pyrexia) or via surrogate markers (e.g. cortisol) When surrogate markers are used their correlation to the clinical effect of the product should be clearly explained in terms of clinical relevance .
- Pharmacokinetics :
- In the context of dose-response relationships, pharmacokinetic data on NSAIDs are considered useful for interpretation of plasma level profiles and related observed effect(s) including potential toxicity linked to dose level and/or treatment duration. Pharmacokinetic studies also support the determination and confirmation of the treatment dose as well as dosing frequency and interval (see section 5.3, PK/PD). It is noted that pharmacokinetic data alone are insufficient for establishing dosing regimens or claims of efficacy for NSAID products: for example, the elimination halflife for a NSAID may differ significantly between plasma and the inflammatory exudate. Furthermore, the correlation between exposure pattern and enzyme inhibition is often weak. As animal species may differ in their response to NSAID treatment, dosages based on results from laboratory animal experiments may not result in similar effects in a target species, and care should be taken when interpreting pharmacokinetic data extrapolated from other species. Therefore, while such studies might provide useful supportive data, pivotal pharmacokinetic studies should be carried out in the target animal species, Pharmacokinetic data could also be useful to explore potential influence of external factors (e.g. feeding) on exposure, if such a relationship is expected.
- Dose determination :
- Dose-determination studies should be conducted in the target species using a range of doses selected on the basis of preliminary studies, parameters that are relevant for the anticipated effect and a dose range that is considered appropriate for further use.
- Preferably, a minimum of three different doses should be included, the central dose being the expected recommended dose. Selection of the higher doses in such studies should take into account the safety margin of the product under investigation. The reason for the choice of doses selected should be explained.
- Dose-determination studies should aim to incorporate not only the dose itself, but also the intended dosing frequency if relevant for a given indication. Alternatively, a PK/PD study may be applied to propose a dose to be further confirmed (see section 5.3). Fewer than three doses may be used in such a study providing that a sufficient exposure range is covered.
- Dose confirmation :
- Dose-confirmation studies should be performed in the target animal species under experimental conditions, using the proposed dose regimen and be conducted with the final formulation. Any deviation should be justified. Dose-confirmation studies may also be performed in the field justified. If a dose range has been selected as a result of dose-dependent differences in clinical effects as claimed, each dose should be studied with respect to its corresponding effect
- Clinical Research : Inclusion criteria for clinical trials in this review pepar included (as a control or primary drug of interest) for the treatment of hand OA . Because of the limited number of studies that used naproxen and OA of the hand only four studies were found .The European union clinical trials interventional clinical trials that are conducted in the European union [EU] and the European economic area EEA clinical trials conducted outside the EU / EEA that are linked to European paediatric medicine development . The EU clinical trials Register displays 42771 clinical trials with a eudra CT protocol of which study performed to investigate the safety or efficacy of a medicine .

- Post marketing monitoring : A post-marketing surveillance case-control study was set up and applied in an Italian hospital network to quantify the risk of upper gastrointestinal bleeding (UGB) and exposure to non-steroidal antiinflammatory drugs (NSAIDs). During the period of study 441 cases of UGB and 1323 controls were recruited. Patients taking naproxen should be monitored for pain relief significant in blood pressure worsening kindly function and GI symptoms such as gastroesophageal reflux disease GERD abdominal pain or melena for patients on chronic NSAID therapy periodic monitoring with complete blood counts to assess kidney and liver function should be considered .
- Human clinical trial : Human clinical trials are conducted on volunteers to evaluate the safety and efficacy of one or more drug agent
- Bioavailability : naproxen is one of the fastly and completely produced in the GI trac with an in vivo bioavailability of 95 % Although naproxen itself is good absorbed .The sodium salt form is more speedily absorbed resulting in greater maximum plasma concentration at specified dose food causes a minor decrease in absorption rate . ❖ Protein binding : Therapeutic levels of Naproxen > 99 % albumin bound Metabolism : Naproxen and parent as well as and metabolites do not cause enzyme metabolizer naproxen is widely metabolized to 6 – 0 desmethyl .
- Half -life : The practically observed elimination of half – life is approximately 15 hours . ❖ Excretion : 0.13 ml / kg clearance of naproxen almost 95 % of the naproxen from any dose is excreted in the urine mostly as naproxen (less than 4 %) 6 – 0 desmethyl naproxen (less than 1 % or their conjugate 66 % - 92 %) .
- Clinical use : Naproxen if used to relieve pain from various circumstances including headache muscle aches . tendonitis dental, suffering and cramps of menstruation .it also decreases arthritis bursitis and gout assaults pain inflammation and joint stiffness
  .
- Toxicology : Naproxen is a overdose is common due to its OTC availability but the overdose is usually mild in serverity and serious adverse effects from overdose are rare . There is available antidote for naproxen overdose monitoring of vital signs and supportive care is recommended .The role activated charcoal is uncertain due to time contraints and unclear benefits and there is no role for hemodialysis due to naproxen s high degree binding .
- Genotoxicity : Genotoxicity is a word used in genetics describes the possession of substance that has destructive effect on genetic material of the cell DNA &RNA thus affecting the integrity of the cell . Genotoxins are mutagents that can cause genotoxicity leading to the damage of a DNA or chromosomal materials thus causing mutation . Genetic toxicology is the branch of science that deal with study of agent or substance that can damage the cells DNA chromosome .
- Safety of NSAIDS / Pharmacology :

  The increasing NSAIDS administration as well as the poor experience with the VIGOR study and identified cardiovascular risk associated with the implementation of the selective inhibitors of cyclooxygenase -2 [Cox-2] shifted the discussion form comparative effectiveness to the administration of nonsteroidal analgesis particularly for patient groups at risk . The regulators did not delay their reaction yet in 2014 several additional safety analysis were initied and the product characteristic of all NSAIDS were obliged to contain a warning concerning the cardiovascular risk associated with their implementation . The intensified medicinal vigilance , though
  ,unambiguously confirmed the optimal safety profile of naproxen containing product .

- Correct patients identification

- Verification + status assessment

- Non pharmacological approaches and local therapy

- Selection of systemic therapeutic approach NSAIDS
- Risk assessment choice of a particular medicinal product
- Recommendations for dose regimen optimal method and duration of NSAIDS administratio
- Concomitant therapy / gastroprotection
- Monitoring of the therapeutic response .
- Algorithm for the choice of therapeutic approach through NSAIDS
- Efficacy of drug : A similar found that 200 mg of naproxen once daily is as effective as 500 mg of naproxen twice daily for arthritis pain and inflammation fever people experienced serious gastrointestinal side effects with naproxen. Naproxen are both effective NSAIDs for pain and inflammation .
- Representative toxicology : Any adverse effect on any aspect of male or female sexual structure and function attestations that affect reproductive system in sexually mature males and females .
- NSAIDS Drug Interaction : NSAIDS is an acronym for non- inflammatory drug alternate names include nonsteroidal anti – inflammatory medicine's (NSAIDS) or non-steroidal anti -inflammatory agents NSAIDS .they are a large class of drugs and include common prescription and over the counter drug naproxen are all examples of NSAIDS.
- Contraindications : Despite the applied evidence from randomized clinical trials and non- interventional post marketing studies of the therapeutic effectiveness and of naproxen there is also a set of contarindication for its use the restriction for its self administration do not differ from those common for NSAIDS .The essential groups of patients where naproxen is not recommended are pregnant women children younger than 12 breastfeeding women and individuals of the whit diagnosed asthma. Naproxen is not sufficiently effective for pains due to endometriosis .
- Design of conduct of observational studies

  Carefully designed and conducted pharmacoeidemiological studies are specifically tools in pharmacovigilance .In observational studies the investigator observes and evaluates results of ongoing medical care without controlling the therapy beyond normal medical practice . Before the observational study that is pharmacovigilance plan commencess a protocol should be finalised . It is recommended that the protocol be discussed with the regulatory authorities before the study starts in also suggested that are the circumstances in which a study should be terminated early be discussed with regulatory authorities in advance .A study report after completion and interim report if approprities according to the milestone whitin the pharmacoeidemiological plans .study protocol should as a minimum include the study aims and objectives the methods to be used an the plan for analysis .The final study report should accurately and completely present the study objectives method results and the principal investigators interpretation of the findings . It is recommended that the sponsor follow good epidemio logical practice for observational studies and also internationally accepted guideline such as the guidelines .

- Selection of drug class
- Commercial availability :

Find here naproxen tablet's, naprosyn manufacturing suppliers and exported in india .A nonsteroidal anti inflammatory drug used as pain reliever and fever reducer Naproxen sodium tablets USP 220 mg had US retail sales of around 316 million as of the re launch is an important addition.

• Selling of drug : Dr Reddy laboratories has re launched over the counter OTC Naproxen sodium tablets USP 220 mg the store brand equivalent of Bayer HealthCare Aleve in US market. Naproxen is classified as a nonsteroidal anti inflammatory drug NSAIDs and was initially approved for prescription use is 1976 and the for over the counter OTC US in 1994.

- India import data :
  Date : 9 Nov 2016
  Indian port : Bombay air cargo
  CTH : 30049099
  Item Description : Naproxen sodium 275 mg film coated tablet (qty :1000 tablet) Quantity : 0.59
  UQC : KGS
  UP USD : 117.35
  Assess USD : 69.24
  Coo : Canada
- Export data :
  Date : 22 Nov 2016
  HS code : 29183090
  Description : NAPROXEN pH EDU (GROUP- A / SRL No : 1011)
  Destination :Poland
  Port of loading : Hyderabad Air Corgo
  Unit : KGS
  Quantity : 100
  Value (INR) : 233,318
  Per Unit (INR) : 2,333
- Mechanism of action : As with other non- selective NSAIDs Naproxen exerts it's clinical effects by blocking Cox-1 and Cox-2 enzymes leading to decreased prostaglandin synthesis . Although both enzymes is contributed to prostaglandin production they have unique functional difference .The Cox-1 enzymes is constitutively active and can be found in normal tissue such as the stomach lining while the Cox -2 enzyme is inducible and produces prostaglandin that mediate pain fever and inflamation. The Cox -2 enzyme mediates the desired antipyretic analgesic and anti inflammatory properties offered by Naproxen while undesired advers effects such as gastrointestinal upset and renal toxicities are linked to the Cox -1 enzyme .
- Indication : Naproxen is indicated for the management of rheumatoid arthritis osteoarthritis ,ankylosing arthritis polyarticular , juvenile ,idiopathic arthritis , tendonitis bursitis and gout primary dysmenorrhea and for the relief of mild to moderate pain . Further it is first line therapy for osteoarthritis acute gouty arthritis dysmenorrhena and muculos keletal inflamation and pain
- Indication advers effect :
- Confusion if Naproxen makes you feel confused speak to you doctor.
- Headache make sure you rest and drink plenty of fluids
- Ringing in the ears changes in vision
- Felling sleepy or tired
- Rashes
- Pharmacological effect
  1) Analhestic action : mild or moderat pain following injury diease or minor surgery as well as chronic pain states including arthritis and cancer .

2) Antipyretic action : NSAIDs reset the set point to the normal level and lower the elevated body temperature in patients with fever by inhibiting the endogenous synthesis of PGs in hypothalamus .

3) Anti – inflammatory action : NSAIDs may provide symptomatic relief from fever, pain and other sign of rheumatic of rheumatoid arthritis but do not arrest the progression of pathological injury to tissue. Some nonselective NSAIDs also have anti – thrombotic action .

- Drug interactions :

Drug interactions may change how your medication work or increase your risk for serious side effect .this document dose not contain all possible drug interactions keep a list of all the products you use (including prescription/ non prescription drug and herbal products) and share it with your doctor and pharmacist. Do not start stop or change the dosage of any medicine's without your doctor's approval .

- Consumer information

What the medication is used for : your health care provider has prescribed Naproxen for you for one or more of the following medical conditions. For the treatment of the sign and symptoms osteoarthritis reheumatoid arthritis and ankylosing spondylitis.
For the relief of minor aches and pains in muscles bones and joint mild to moderate pain compaied by inflammation In sprains and strains and primary dysmenorrhea.

What it dose : Naproxen as a non- steroidal anti – inflammatory drug NSAIDs can reduce the chemical products by your body which casue pain and swelling . Naproxen as a non steroidal anti – inflammatory drug NSAIDs does not cure your illness or prevent it from getting wires . Naproxen can only relive pain reduce swelling as long as you continue to take it .

When it should not be used : Do Not Take Naproxen if you have any of the following medical conditions. heart bypass surgery (planning to have or recently had) .

Sever uncontrolled heart failaure .

Bleeding in the brain or other bleeding disorders .

Current pregnancy (after 28 weeka of pragnancy) currently breastfeeding or planning to breastfeed .

Allergy to ASA (acetylsalicylic acid) or other NSAIDs ulcer active .

Bleeding form the stomach or gout active .

Inflammatory bowel disease (crohn's disease or ulcerative colitis) .

Liver disease (active or severs) .

Kidney disease (severe or worsening) .

High potassium in blood.

Naproxen should not be used in patients under 18 years of age since the safety and effectiveness have not been established.

What the medicinal ingredient is : Naproxen

What dosage forms it comes in : Naproxen is available as immediat release tablets (250 mg – 375 mg and 500 mg)

Over dose : If you think you or person you are caring for have takn too much Naproxen contact a healthcare , professional, hospital emergency department or regional poison control centre immediately even of there are no symptoms. How to store it : store at room temperature (15 – 30°c) store in a dry place .Do not keep outdated medicine no longer needed.any outdated or un used medicine should be returned to your pharmacist .

• Pharma companies web portals :

Headquartered in Hyderabad India Dr Reddy laboratories is one of the leading active pharmaceutical ingredients API manufacturers and suppliers globally for naproxen sodium. API Dr Reddy's API business is a preferred partner to Pharma companies across to the US , Europe , Brazil,latin, America, japan, china,korea , middle East, and other emerging markets .

Identification of Advers effects of a selected drug (Naproxen)

• Common side effects of Naproxen

Higher risk of having a heart attack or stroke (especially in smoker those who take it for a long period of time and those who have a family history of heart diease or high blood pressure) .
Ulcers bleeding and holes in the stomach or intestines (especially if your are older or drink more than 3 glasses of alcohol per day).
Colon problem (diarrhea , constipation,gas).

Sores in the mouth .

Excessive thirst.

Headache

Dizziness

Lightheadedness

Drowsiness

Serious side effects : sever indigestion heartburn pains in your stomach feeling or being sick (nausea or vomiting or diarrhoea these can be signs of an ulcer or swelling (inflammation) in your stomach or gut .

- Vomiting blood or dark particles that look like coffee grounds blood in your poo, or black poo that look like tar these could be signs of bleeding and perfomation of your stomach or gut .
- Feeling faint tired or short of breath these can signs of anaemia.
- Blood in your pee passing less pee feeling or being sick these can be signs of kidney damage or infection.
- A high temperature stomach pain and being sick these can be signs of inflammation of the pancreas.

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. :

Report Type ☐ Initial ☐ Follow up

Worldwide Unique No. :

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	Unknown	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):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

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