IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Study of Ibuprofen Drug Related with Pharmacovigilance.

1st Author : Kshirsagar Tejas Girijaprasad ,2nd Author : Prajakta Balu Paimode, 3rd Author : Karjule Shreyas Gorakshnath, 4th Author : Padule Amol Rajaram, 5th Author : Rokade Rutuja Jagdish

Department of 1st author: D. Pharmacy, Pune, India

Abstract :-

Pharmacovigilance refers to the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects and other drug-related safety problems. Related to this general definition, the underlying objectives of pharmacovigilance are to prevent harm from adverse reactions in humans that arise from the use of health products within or outside the terms of marketing authorization and in relation to the life cycle of these health products.

The main goal of pharmacovigilance is thus to promote the safe and effective use of health products, in particular by providing timely information about the safety of health products to patients, health-care professionals, and the public. Pharmacovigilance is therefore an activity contributing to the protection of patients and maintaining public health.

This article summarizes the main pharmacological effects, clinical and preclinical trial therapeutic applications and adverse drug reactions, drug-drug interactions and food drug interactions of ibuprofen that have been consumption report selling of drug throughout India . Therapeutic uses pharmacokinetic and dynamic study and their safety efficacy and genotoxicity.

Ibuprofen is a traditional nonsteroidal anti-inflammatory drug (NSAID) widely used for its analgesic, anti-inflammatory, and antipyretic properties [1,2]. At low over-the-counter doses (800–1200 mg/day), ibuprofen is indicated to relieve minor pain and inflammation, including headache, muscular aches, toothache, fever, backache, and dysmenorrhea. At prescription doses (1800–2400 mg/day), it is used for the long-term treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and other chronic conditions.

❖ CLINICAL RESEARCH.

☐ 1. Definition and phases of clinical trials.

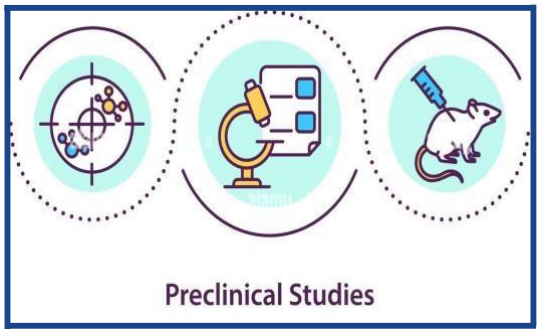
➢ **Definition and introduction**:-

- Clinical trials are a type of research that studies new tests of treatment and evaluate their effects on human health.
- People volunteer to take part in clinical trials to test a medical intervention including drugs, cells,& other biological products, surgical procedures and other radiological processes, devices, behavioural treatment & preventive care.
- Clinical trials are carefully designed, reviewed and complete and need to be approved before they can start.
- People of all ages can take part in clinical trials, including children.
- It is a systematic investigation in human subjects for evaluating the safety and efficacy of any drug.
- It is a set of tests in medical research and drug development that generates safety and efficacy data for health intervention in human beings.

➢ **There are mainly two types in clinical research. 1) Preclinical trial.**
2) Clinical trials

1) Preclinical trials.

In the preclinical trials we study about the animals. Which under the ICH [M3] guidelines.



- The non clinical means the preclinical studies are discussed under the ICH[M3] guidelines, for the recommendation for the marketing Approval of a pharmaceutical products include.

1) Safety pharmacology studies.
2) Repeated dose toxicity.
3) Toxicokinetic.
4) Non-clinical.
5) Reproduction toxicity.
6) Genotoxicity.

- Animal safety studies & human clinical trials should be designed to represent scientifically and ethically.

➢ **Preclinical trial studies about the mentioned below**.

1) Safety pharmacology
2) Toxicokinetic and pharmacokinetic studies.
3) Acute toxicity studies
4) Repeated dose toxicity
5) Local tolerance studies
6) Genotoxicity studies
7) Carcinogenicity
8) Reproduction toxicity
9) Other toxicity

2) Clinical trials:-

Clinical trials should be studied in humans which are under the ICH[E3] guidelines which refer to the structure and content of clinical trials which study report section 12 of the guidelines deal with safety evaluation.

- The definition of other significant adverse events include; haematological and other laboratory abnormalities and any adverse event that led to an intervention including withdrawal of drug treatment dose reduction or significant concomitant therapy.

➢ **Classifying clinical studies according to objective.**

Type of study	Objective	Study example
1) Human pharmacology	Asses tolerability described pk pd explore drug metabolism & drug interactions.	Dose tolerability single & multiple dose pk & pd & drug interactions.
2) Therapeutic exploratory.	● Explorer used for the targeted indication. ● Estimate dosage for subsequent study. ● Provide a basis for end point methodologies..	● Earliest trial of relatively short duration. ● Dose response exploration studies.
3) Therapeutic use	● Understanding of benefit; risk relationship in general or special populations. Identify less common ADR.	● Study of mortality morbidity. ● Large sample trial. ● Pharmacoeconom ic study.

➢ **Types of clinical trials**:-

Clinical trials should be conducted and analysed according to its sound scientific principles, with due regard to ethical considerations in order to achieve the trial objective.

- There are various types of clinical phases.

1) Phase 0 trial.
2) Phase 1.
3) Phase 2.
4) Phase 3.
5) Phase 4.

Phase 0 trial :-

Objective	Therapy area.	Dosage.	Trial length.	Patient.
Measure pk/ toxicity in human before phase;1 improve preclinical candidate selection	Any indication.	Subtherape uric dosing. (Normally micro dosing)	Usually less than 1 week.	Phase 0 of a clinical trials is done with a very small number of people usually fewer than 15.

2)Phase 1 trial:-

Objective.	Trial length.	Patient.	Purpose.
-The main aim of the phase -1 trial is to find out about doses and side effects .	1 month to 1 year.	20-80.	Safety and efficacy of dosage.
-Some people taking part may benefit from the new treatment but mainly won't.			

3) phase 2 trial :-

Objective	Trial length	Patient	Purpose
-An phase 2 clinical trials tell doctors more about how safe treatment is and how well it works. -Doctors also test whether a new treatment works for a specific cancer. -They might measure the tumour's, take blood samples, or check how well they do activities.	Several months to 2 years.	100-300.	Efficacy and side effects.

4) phase 3 trial:-

Objective	Trial length	Patient	Purpose
The main objective of phase 3 is to verify the therapeutic action of a nee substance in a large number of patients essential to determine the risk ratio.	1 to 4 years.	300 to 3000 volunteers who have the disease conditions.	Conformity and monitoring ADR.

5) phase 4 trial:-

Objective	Trial length	Patient	Purpose
This trial was studying the side effects caused overtime by a new treatment after it has approved in the market . -This trial looks like a side effect that was not seen in the earliest trial related study of a new treatment work over a long period.	Typically they are conducted for a minimum of 2 years .	Several thousand volunteers teer who have disease conditions.	ADR & post marketing surveillance.

☐ **2. Function of drug controller India(DCGI) & Central drug standard control organization (CDSCO).**

➢ **DCGI** :-

- Preparation and maintenance of national reference standards.
- To bring about uniformity in the enforcement of the drug and cosmetics act.
- Training of drug analysts deputed by state drug control laboratories and other institutions.
- Analysis of cosmetics received as survey sample free CDSCO.

➢ **CDSCO**:-

- Approval of new drug and clinical trial.
- Import registration and licensing .
- License approving of blood bank ,lupus, vaccine,r-dna, product and some medical devices.
- Testing of a new drug.
- Grant of test license, personal license,NOC s export . ● Banning of drug & Cosmetic act.

☐ **3. Types of regulatory application:- investigational new drug (IND), New drug Application (NDA), Abbreviated new drug application (ANDA).**

➢ **IND** :-

- The identity and contact information of the sponsor and the phase of trial.
- A commitment that an IRB will be responsible for initial and continuing review of the trial.
- The name of the drug list of its activities ingredients and its dosage and route of administration.
- The objective and planned duration of the proposed clinical trials.

➔ Duration :-

An IND application may go into effect 30 days after FDA receives the application, unless FDA notifies the sponsor that the investigation described in the application is subject to a clinical hold or on earlier notification by FDA that the clinical investigator in the IND begins .

➢ **NDA :-**

- An application submitted by the manufacturer of a drug to the FDAafter clinical trials have been completed for a license to market the drug specified.
- New drug application (NDA) is the vehicle in the United States through which drug sponsors formally propose the FDA approved.
- The data gathered during animal studies & human clinical trials of an investigational new drug (IND) become part of the NDA.

➔ Duration:-

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

➢ **ANDA :-**

- An application for a license to market a generic (or a duplication) version of a drug that has already been granted an approval under a full NDA.

i.e. the drug has already met the statutory standard for safety and

effectiveness.

● A generic drug product is one that is comparable to an innovator drug product in dosage form strength, route of administration quality, performance characteristics and intended use.

●

➔ Duration :-

This act also permits brand- name companies to apply for exclusive patent rights to cover their new drug upto 5 years.

❖ Good clinical practice.

☐ Objective :-

- To provide an overview of the history of a good clinical practice (ICH).
- To emphasize the importance of ICH GCP compliance when conducting clinical trials.
- To recognise implications of non- compliance.
- To review positive and negative cause studies.
- Avoid trial duplication (saving the memory resources).
- The trial requirements for medicinal products containing new.

☐ Scope of GCP:-

Good clinical laboratory should be used by all laboratories, where tests are done on biological specimen diagnosis, patients cure , disease cannol.

- Microbiology and serology.
- Haematology and blood banking.
- Molecular biology and molecular pathology.
- Clinical pathology.
- Histopathology.
- Studies physiological biochemical and pathological process of the response to a specific intervention whether physical and chemical.

❖Concept of pharmacovigilance.

☐1. Definition , objective , type and components of pharmacovigilance.

➢ **Definition :-**

Pharmacovigilance is the science and activities relating to the detection , assessment, understanding, and prevention of adverse effects or any other medicine / vaccine rated problem for patients safety.

➢ **Objective:-**

- Improvement of patients care and safety in relation to the use of medicine and paramedical intervention remains to be an important parameter.

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

➢ **Types.**

There are four types of pharmacovigilance.

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

1. 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.

- **Examples of spontaneous reporting systems include the -**
- 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.

2.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.

3.cohort event monitoring :this method, the surveillance study is planned prior to beginning the treatment with the medication. A group of people are exposed to a 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.

4.Targeted clinical investigation:-

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

☐ **Components :-**

- Adverse Event Case Management Including Expedieted Report
- EU pharmacovigilance laws mean that ALL spontaneous reports regarding serious adverse reactions must be expedited within 15 days. In addition, as of 22nd November 2017 all non-serious adverse reactions, with an origin within the EU, require expediting to EMA within 90 days. Fact:
- These laws will mean that ALL suspected reactions provoked by a medicinal product must be expedited – regardless of seriousness. Expedited reports
- Remaining compliant throughout all the changes to EU legislation can be a challenging endeavour for any company. This is particularly the case with Expedited Reporting – one of the pillars of all EU pharmacovigilance work. Fact:
- EU pharmacovigilance laws mean that ALL spontaneous reports regarding serious adverse reactions must be expedited within 15 days. In addition, as of 22nd November 2017 all non-serious adverse reactions, with an origin within the EU, require expediting to EMA within 90 days. Fact:
- These laws will mean that ALL suspected reactions provoked by a medicinal product must be expedited – regardless of seriousness. Fact:
- One of the most common causes of critical findings in Drug Safety Inspections is non-compliance with the expedited reporting of spontaneous adverse drug reactions.
- Non-compliance can result in time-consuming and costly remedial work and/or penalties imposed by regulators. These can include inspections, CAPAs, and suspensions of Marketing Authorisations. What Is Expedited Reporting?
- In the EU post-marketing environment, an Individual Case Safety Report (ICSR) may involve a serious or non-serious adverse reaction – regardless of expectedness. Such cases must be submitted to the regulatory authorities within 15 days or 90 days respectively. As a Marketing Authorisation Holder, you need to be fully versed in each change to the drug safety laws in concerned territories around expedited reporting as and when it happens. With regards to these updates, you as the Marketing

Authorisation Holder need to implement them to remain fully compliant. With the right support, you can rapidly respond to the challenges in line with your Standard Operating Procedures.

➢ **Post-Marketing Phases**

● 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.

➢ **Aggregate Reporting**

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

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

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

● Why aggregate reporting is important?

● Though the Individual case safety reports were submitted on expedited basis to regulatory authorities, detailed analysis and evaluation of benefit/risk ratio of a drug is not possible at this level. Therefore periodically reviewing safety reports received cumulatively worldwide, becomes highly significant to analyse 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: Pre-marketing report:

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

➢ **Signal Detection and management in Pharmacovigilance.**

● Pharmacovigilance involves the collection of data on Adverse Reactions which must then be analysed and evaluated to create meaningful safety information.

● 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 to generate them.

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. The definition of a signal as provided by the CIOMS Working Group 8 is:

● information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action".

● This could be a problem which has never previously been suspected to be associated with the product; or a known event which is now occurring within a patient group for whom it has not been documented before or perhaps occurring with greater frequency than anticipated. The signal may be generated from qualitative analysis of spontaneous reports or quantitative analysis through data mining and statistical activities.

➢ **What Is 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) ● metaanalyses (i.e. mathematical pooling of all the clinical trial data) ● other relevant sources.

➢ **Risk Management**

● Risk management in pharmacovigilance is undertaken to promote safe use of medicines and safeguard health of patients. It is a set of activities performed for identification of risk, risk assessment, and risk minimization and prevention. Risk management has the following stages: identification and characterization of the safety profile of the medicinal product;

planning of pharmacovigilance activities to characterize risks and identify new risks; planning and implementation of risk minimization and mitigation and assessment of the effectiveness of these activities; and document post approval obligations that have been imposed as a condition of the marketing authorization.

- All these activities together constitute the risk management plan, which is required to be submitted during the authorization of the drug. The overall aim of risk management is to ensure that the benefits of the medicinal product outweigh the risks by a wide margin for the treatment of a particular indication both at individual level and for the target population as a whole.2) Constitutional objective of pharmacovigilance 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.

➢ **Pharmacovigilance Programme of India (PvPI):-**

- The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in collaboration with Department of Pharmacology, All India Institute of

Medical Sciences (AIIMS), New Delhi has launched the nation-wide

Pharmacovigilance programme for protecting the health of the patients by assuring drug safety. The programme is coordinated by the Department of Pharmacology at AIIMS as a National Coordinating Centre (NCC).

➢ **Constitutional objective of pharmacovigilance 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.

➢ **Pharmacovigilance Programme of India (PvPI):-**

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

➢ **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 centre of excellence at par with global drug safety monitoring standards.

B)list of national adverse drug monitoring centres(AMCS) and their functions. National Coordinating Centre (NCC):-

Address :-Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.

Coordinators :- Dr. Y.K. Gupta National Coordinator

ADR Monitoring Centres (AMC) :-

Sr.no.	Address	Coordinators
01.	Department of Pharmacology, Therapeutics & Toxicology, Govt. Medical College, Bakshi Nagar, Jammu.	Dr. Vishal Tandon
02.	Department of Pharmacology, PGIMER, Chandigarh	Dr. Bikash Medhi

03.	Department of Pharmacology, R.G. Kar Medical College, Kolkatta	Dr. Anjan Adhikari
04.	Department of Pharmacology, Lady Hardinge Medical College, New Delhi	Dr. H.S. Rehan
05.	Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, Parel, Mumbai	Dr. Urmila Thatte
06.	Department of Clinical & Experimental Pharmacology, School of Tropical Medicine, Chittaranjan Avenue, Kolkata	Dr. Santanu Tripathi
07.	Department of Pharmacology, JIPMER, Pondicherry	Dr. C Adithan
08.	Department of Clinical Pharmacy, JSS Medical College Hospital , Karnataka	Dr. Parthasarathi G
09.	Department of Pharmacology , Medical College , Guwahati. Assam	Dr. Mangala Lahkar
10.	Himalayan Institute of Medical Sciences, Dehradun, Uttrakhand	Dr. DC Dhasmana
11.	Department of Clinical Pharmacology, Christian Medical College,Vellore, Tamil Nadu	Dr. Sujith chandy

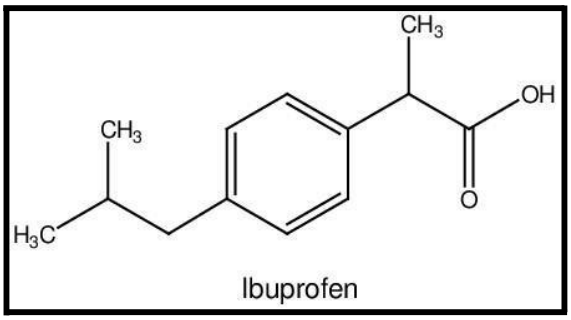
➢ **Function of AMC**

- To monitor the ADR.
- TO Optimize safe and effective use of medicines in over set up.
- To create awareness amongst healthcare professionals about the importance of ADR Reporting.
- To monitor benefits risk profile of medicines.
- Generate independent, evidence based recommendations on the safety of medicines.
- Support the CDSCO for formulating safety related regulatory decision for medicines.
- Communicate finding with all key stakeholders.
- Create a national center of excellence as per with global drug safety monitoring standards.

➢ Safety monitoring during clinical trials. ❖ Drug :- Ibuprofen.

● Ibuprofen is a non - steroidal anti - inflammatory drug [NSAID] ● It is used for treating pain, fever and inflammation.

- This includes painful menstrual period , migraines and rheumatoid arthritis.
- It may also be used to close patent ductus arteriosus in a premature baby.
- It can be used by mouth or intravenously. ● It typically begins working within an hour. ➢ **Structure :-**



Ibuprofen

➢ **Route of administration:-**

By mouth, rectal , topical intravenous.

➢ **Brands :-**

Ibuprofen is sold under a wide variety of brand names across the world ; the most common being its first register trademarks name of brufen ,along with advil ,motrin , and nurofen.

☐ **List of brand :-**

- Advil :- Tablet, capsule , liquid, liquid filled capsule.
- Combiflam :- Tablet.
- Brufen:- Tablet, oral syrup, miscible granule.
  - Tablet :- 200mg, 400mg, 600mg.
    - Syrup :- 100mg,/ 5ml.
    - Granules:- 600 mg / sachet.
- Calprofen:- oral syrup . 100mg,/ 5ml.
- Cebupac :- tablet. 200mg,400mg,600mg.
- Faspic:- tablet, 200mg,400mg.
  - Philippians the cathay drug company inc. ● Besiflam :- tablet.

➢ **History :-**

- The invention of ibuprofen arose out of a boots study to treat rheumatoid arthritis before evolving into a drug to relieve a range of conditions.
- Ibuprofen was discovered in 1961 by dr.stewart adams and john nicholson while working at boots UK limited and initially marketed as brufen.
- It is available at trade names.
- Ibuprofen was first marketed in 1969 in the United Kingdom and in 1974 in the United States.
- Over the counter version available from 1983.

➢ **Clinical trials :-**

➢ **The clinical trials are conducted by giving the ibuprofen showing in the following survey.**

- Aims

The GI safety and therapeutic efficacy of Ibuprofen chemically associated with phosphatidylcholine (PC) was evaluated in osteoarthritic (OA) patients.

- Methods

A randomized, double-blind trial of 125 patients was performed. A dose of 2400 mg/day of ibuprofen or an equivalent dose of Ibuprofen-PC was administered for 6 weeks. GI safety was assessed by endoscopy. Efficacy was assessed by scores of analgesia and anti-inflammatory activity. Bioavailability of ibuprofen was pharmacokinetically assessed.

- Results

Ibuprofen-PC and ibuprofen provided similar bioavailability/therapeutic efficacy. In the evaluable subjects a trend for improved GI safety in the Ibuprofen-PC group compared with ibuprofen was observed, that did not reach statistical significance. However, in patients >55 years of age, a statistically significant advantage for Ibuprofen-PC treatment vs ibuprofen in the prevention of NSAID-induced gut injury was observed with increases in both mean Lanza scores and the risk of developing > 2 erosions or an ulcer. Ibuprofen-PC was well tolerated with no major adverse events observed.

- Conclusions

Ibuprofen-PC is an effective osteoarthritic agent with an improved GI safety profile compared to ibuprofen in older OA patients, who are most susceptible to NSAID-induced gastroduodenal injury.

➢ **Preclinical trial :-**

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), showed very promising neuroprotection action, but it suffers from high first pass metabolism and limited ability to cross blood brain barrier. Severe gastric toxicity following oral administration further limits its utility. Hence, the aim of this study was to investigate whether ibuprofen loaded mucoadhesive microemulsion (MMEI) could enhance the brain uptake and could also protect the dopaminergic neurons from MPTP-mediated neural inflammation. In this work, ibuprofen loaded polycarbophil based mucoadhesive microemulsion (MMEI) was developed by using response surface methodology (RSM). Male C57BL/6 mice were intranasally given 2.86 mg ibuprofen/kg/day for 2 consecutive weeks, which were pre-treated with four MPTP injections (20 mg/kg of body weight) at 2 h interval by intraperitoneal route and immunohistochemistry was performed. Globule size of optimal MMEI was 46.73 nm ± 3.11 with PdI value as
0.201 ± 0.19. Histological observation showed that optimal MMEI was biocompatible and suitable for nasal application. The result showed very significant effect ($p < 0.05$) of all three independent variables on the responses of the developed MMEI. Noticeable improvement in motor performance with spontaneous behaviour was observed. TH neurons count in substantia nigra with the density of striatal dopaminergic nerve terminals after MMEI administration. Results of this study confirmed neuroprotection action of ibuprofen through intranasal MMEI against MPTP induced inflammation in dopaminergic nerves in animal model and hence, MMEI can be useful for prevention and management of Parkinson disease (PD).

➢ **Pharmacokinetic :-** Drugs do to the body .
(ADME)

☐ **Absorption :-**

The absorption of ibuprofen is rapid and complete when given orally . ● Prescribed dose of ibuprofen.

- Adult :- 200-800 mg every 6-8 h. ● Pediatric:- 5-10 mg every 6-8 h.
- An intravenous formulation is also approved for use in the USA.
- Ibuprofen is administered as a racemic mixture of R and S enantiomers with S - ibuprofen being largely responsible for its pharmacologic activity.
- R - ibuprofen inversion to the S - enantiomers through an acyl- COA thioester by the enzyme a- methylacyl - coenzyme.

☐ **Distribution:-**

- Ibuprofen binds extensively in conc. depend on plasma albumin (200 - 400 mg).
- At doses greater than 600 mg there is an increase in the unbound fraction of the drug leading to an increased clearance of ibuprofen.
- IBU exhibits a lower apparent volume of distribution that approximate plasma volume (0.1 - 0.21)kg).
- But it is able to penetrate into the central nervous system and accumulate at peripheral sites where its analgesic and anti - inflammatory effects are required.
- Ibuprofen is present in cerebrospinal fluid and in the synovial fluid in the inflamed joint of arthritis.

☐ **Metabolism :-**

- Metabolism occurs mainly in the liver and sometimes in gut also.
- Ibuprofen is almost completely metabolized with little to no unchanged drug found in the urine.

☐ **Excretion :-**

- Urinary excretion of the two major metabolites ,carboxy - ibuprofen and 2hydroxy ibuprofen and their corresponding acyl glucuronides.
- CYP2C9 is the primary CYP isoform responsible for ibuprofen clearance.

☐ **Transport :-**

- Organic anion transporter in the kidney & GI tract . ● Hepatic organic anion transporter.
- Multi drug resistance protein family (MRPs). ● The intestinal peptide transport.

☐ **Pharmacokinetic data:-**

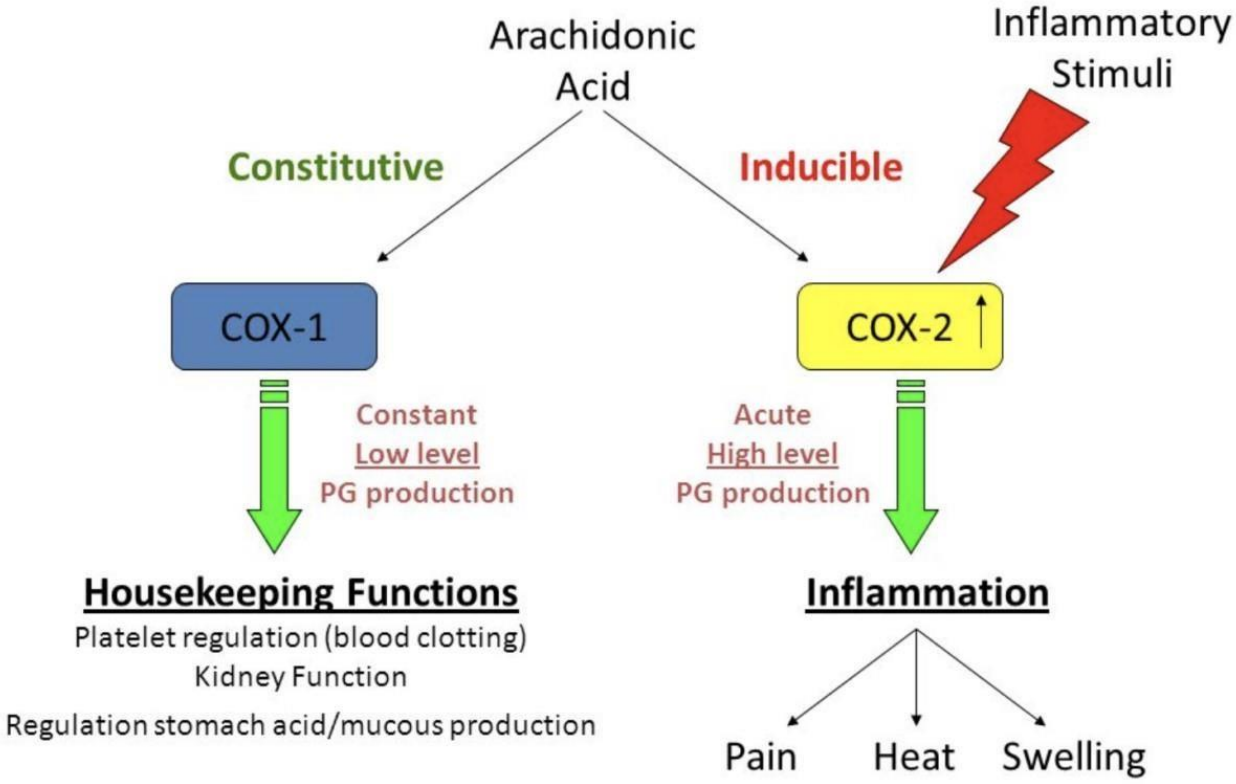
Bioavailability	80-100% by mouth.87% rectal.
Protein binding	98%.
Metabolism	Liver.

Onset of Action	30 min.
Elimination of half life	2-4 hr.
Excretion	Urine -95%.

➢ **Pharmacodynamic :**Body does drugs.

- The main mechanism of Action of Ibuprofen is the non- selective, reversible inhibition of the cyclo-oxygenase enzymes Cox-1 & cox -2.
- COX-1 & cox-2 catalyze the first committed Step in the synthesis of prostaglandin (PG) €2 PGD 2, PGF2 a pGl2 (also known at prostacyclin) and thromboxane (TX) A2.
- prostaglandin are found in Inflammatory exudates and can reproduce the cardinal Signs of inflammation including paint.
- They are generated from arachidonate by action of cyclooxygenase (cox)isoenzymes.

➢ **Mechanism of Action :-**



➢ **Ibuprofen side effect :-**

- Ibuprofen appears to have the lowest incidence of digestive Adverse effect reaction of all the non-selective NSAID.
- Nausea, Dyspepsia gastrointestinal ulceration, bleeding, diarrhoea, constipation and Hypertension.

➢ **Contra - indication :-**

- Ibuprofen tablet are Contra-indicated to patient with known hypersensitivity to ibuprofen.
- Asthma.
- Hypertensive patient ● Heart attack.
- stomach or Intestinal ulcer
- Liver problem and Blood clotting disorders ● Bleeding of the stomach or intestines.
- kidney disease .
- pregnant in 3rd trimester.

➢ **Uses :**● Fever.

- Inflammation.
- Headache.

- Toothache.
- Back pain.
- Arthritis.
- Minor injuries.

➢ **Ibuprofen in dentistry :-**

- Analgesic medications in dentistry are indicated for the relief of Acute pain, postoperative pain & chronic pain.
- Endodontic pain management pain control particularly during the early phases of endodontic treatment.
- wisdom tooth extraction managing post-operative pain.
- pediatric dentistry for relieving moderate to Severe pain. They found that single dose of Ibuprofen (4-10 mg/kg)
- Orthodontic pain management pain and discomfort are common clinical symptoms for orthodontic patients, especially 2 to 4 days after the placement of fixed orthodontics application.
- periodontal pain management; Chronic periodontitis is a Common inflammatory disease Gingiva.

➢ **Uses in dentistry :-**

- The Combination of 600mg of ibuprofen with 1000 mg of paracetamol taken every six hours Increases pain relief compared with ibuprofen taken alone.
- Ibuprofen and Codeine (which enhances ibuprofen analgesic but with a increase in adverse effect)
- use of absorption gel Capsule that provides faster and therefore a quicker effect.

➢ **Ibuprofen drug interactions :● ACE inhibitors:-**

NSAID may diminish the antihypertensive effect of ACE inhibitors.

- **Aspirin :-**

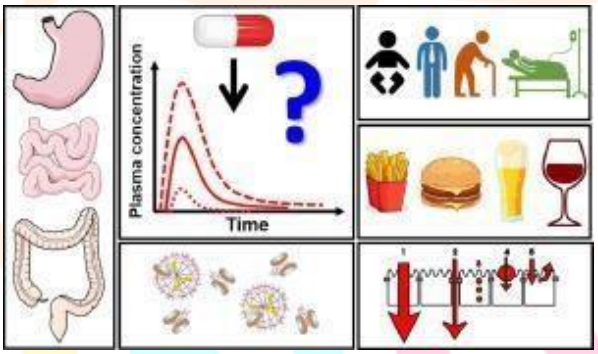
Administration of ibuprofen and aspirin is not generally recommended because of the potential for increased ADR effect.

- **Diuretic :**

Ibuprofen Can reduce the natriuretic effect of furosemide and thiazide Some observed patients in the patient should be observed closely for signs of failure as well as to assure diuretic efficacy.

- **warfarin type anticoagulant :-** users of both drugs together have a risk of serious bleeding higher than users of either ding alone.

➢ **Ibuprofen interaction with food and herbs :-**



- Cannabis sativa :

Ibuprofen may interact marijuana to increase the risk of bleeding ● interactions with Alcohol:
Ibuprofen interacts with alcohol due to this interaction, stomach bleeding Severe liver damage may arise.

➢ **How to take the medication :-**

○ Ibuprofen should be taken with milk or food to reduce the chances of stomach irritation.

➢ **Toxicology :-**

Ibuprofen is a NSAID that reduces level of the hormone that cause pain, inflammation, swelling and fever it is used to treat condition such at toothache headache arthritis, back pain menstrual cramps.

➢ **Symptoms of toxicity from ibuprofen :-**

1) G.I effect :-

GI blood loss due to fen intake occurs in a dose related manner. This blood loss occurs in up to 17% of patients who receive 1600 mg per day and in almost a quarter of those who receive 2.400mg Per day.

- in that include effect :- nausea, vomiting, dyspepsia, diarrhoea, flatulence.

2)Effect on the liver:-

Elevations in liver are found in upto 15% of patients the hepatic side effect cholesterol, hepatitis Jaundice & hepatic failure have to rarely been Reported.

- patients with liver disease require regular liver function tests When they are receiving ibuprofen, Ibuprofen induced hepatitis can lead to fatality.

▪

3) Renal effect :-

Renal side effects include urinary retention, renal insufficiency, acute "failure, nephrotic Syndrome and acute tubular necrosis.

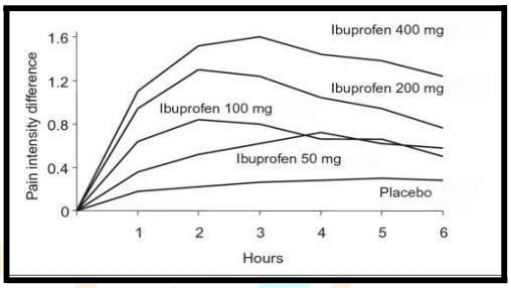
4)Ocular effects :example of ocular side effect include blurred vision. scotomata and diplopia. ➢ **Genotoxicity:-**

Genotoxicity of ibuprofen was evaluated by employing the mouse in vivo chromosomal aberration (CA) test. Ibuprofen administered orally at doses of 10, 20, 40, and 60 mg/kg body weight to mice resulted in mitotic depression and induction of

CAs. A dose-related decrease in mitotic index (MI) and an increase in the

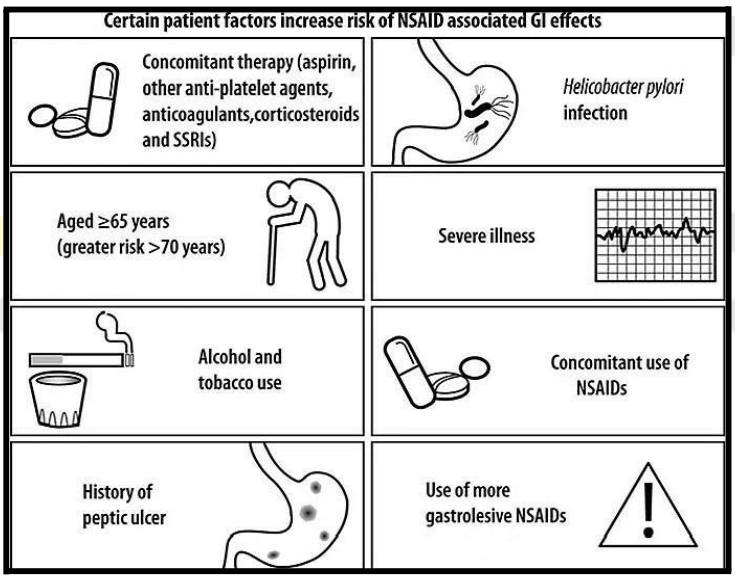
frequencies of chromosomal aberrations per cell (CAs/cell) were recorded in bone marrow cells. However, a statistically significant reduction in MI and an increase in CAs/cell were found for both the higher doses. The results obtained indicate that ibuprofen is capable of inducing dose-dependent genotoxicity in bone marrow cells of mice.

➢ **Efficacy:-**



- There is a clear relationship between single doses of ibuprofen over the range 50-400 mg and the peak analgesic effect and the duration of analgesia.
- The smallest clinically useful dose of ibuprofen is 200 mg.
- Ibuprofen 400 mg has been shown to be as effective as aspirin 600 or 900 mg/day in models of moderate pain but superior to aspirin or paracetamol in more sensitive models such as dental pain.
- The duration of action of ibuprofen 400 mg is at least 6 hours compared with 4-6 hours for ibuprofen 200 mg or paracetamol. In patients undergoing oral surgery, ibuprofen 200 mg was broadly comparable with naproxen 220 mg and ibuprofen 400 mg comparable with ketoprofen 25 mg.
- The combination of ibuprofen and hydrocodone is more effective than either drug alone in patients undergoing abdominal and gynaecological surgery.
- The absorption of ibuprofen acid is influenced by formulation, and certain salts of ibuprofen (lysine, arginine, potassium) and solubilised formulations have an enhanced onset of activity. These differences are clinically important, offering a shorter time to onset of relief of tension headache compared with paracetamol.

➢ **Safety :-**



- This assessment of the safety and benefits of ibuprofen:-

(1)Ibuprofen at OTC doses has low possibilities of serious GI events, and littleprospect of developing renal and associated CV events. Ibuprofen OTC does not represent a risk for developing liver injury, especially the irreversible liver damage observed with paracetamol and the occasional liver reactions from aspirin.

(2)The pharmacokinetic properties of ibuprofen, especially the short plasma half-life of elimination, lack of development of pathologically related metabolites (e.g. covalent modification of liver proteins by the quinine–imine metabolite of

paracetamol or irreversible acetylation of biomolecules by aspirin) are support for the view that these pharmacokinetic and notably metabolic effects of ibuprofen favour its low toxic potential.

(3)The multiple actions of ibuprofen in controlling inflammation combined with moderate inhibition of COX-1 and COX-2 and low residence time of the drug in the body may account for the low GI, CV and renal risks from ibuprofen, especially at OTC doses.

➢ **Ibuprofen has a wide therapeutic use of classes:**● Anti-inflammatory effect: modification of inflammatory reaction via decreases in vasodilator prostaglandins.

- Analgesic effect : reduction of certain Sorts of pain via reduced sensitivity of nerves to certain inflammatory mediators.
- Antipyretic effect:

lowering of a raised temperature via decrease in a mediator Prostaglandins
which is responsible for elevating the hypothalamic temperature control.

➢ **Selection of drug class:-**

☐ 1. Selection of drug class for pharmacovigilance study using different criteria (eg.commercial availability. Selling of drug.)

➢ **Availability:-**

❖ **Ibuprofen :-**

Ibuprofen is available in many forms.

- Tablet.
- Capsule.
- Liquid.
- Gels or cream.
- Sprays. ● IV, IM.
- It is a painkiller available over the counter without prescription .
- It is a one of the group painkillers that is called a non steroidal antiinflammatory drug.

➢ **Available:-**

- Ibuprofen was discovered in 1961 by Stewart Adams and john nicholson while working at boots uk limited and initially marketed as brufen.
- It is available under a number of trade names, including nurofen, advil & motrin.
- Ibuprofen was first marketed in 1969 in the United Kingdom and in 1974 in the United States.

☐ **Selling of drug:-**

- In 2019 the ibuprofen market size was estimated around $ 573 million.
- The high production cost and comparatively lower margin level in ibuprofen API resulted in lower sales in 2019 due to a 20-30 % price spike in final drug production.
- AS an Over the Counter drug ibuprofen ia a popular painkiller that is also used to treat fever.

The demand for ibuprofen is seeing a steady rise.

- It has been observed that developed geographies like the US and Europe. have a higher demand for ibuprofen than the developing side of the World.
- Even though scoring low in demand capability, developing nations are leading the supplier market , becoming global ibuprofen exposure.
- As the world's major manufacturers of API ,China supplies 90% of the US ibuprofen requirements.
- Whereas India exports around 493 tons of ibuprofen API to the UK and Ireland.
- India and the US are the leading supply centers for ibuprofen API .
- All the major stakeholders with bulk supplying and manufacture capacity are located in this region capturing 70% of the global market.

☐ **Though COVID-19 had stagnated the production of API, affecting the ibuprofen market industry:-**

- manufacturers are growing their production capacities to bridge the demandsupply crunch globally.
- China has now resumed manufacturing APIs of the top-selling drugs, including Ibuprofen.
- The high cost of raw material in 2020 has led to an elevation in the price of Ibuprofen across the global ibuprofen market.
- The increasing API drug shortage has pushed China to increase the prices of these APIs by 22 percent.

☐ **Upscaling the production capabilities is the main strategy defined to ease the increasing demand for the Ibuprofen API.**

- In addition to this, the manufacturing-friendly regulatory provision and lower taxation policies promote establishing Ibuprofen API manufacturing businesses and are fueling the growth of the Ibuprofen API market in East and South Asia.
- Further, the low labour cost and easy availability of raw materials for Ibuprofen API are also enabling the growth of the Ibuprofen market in the South Asian regions.

● With the rise in the number of patients in the South and East Asia region consuming non-controlled drugs, these supplying markets are soon to gain strong buying power.

➢ **Key findings** :-

1) In 2019, the revenue of the global Ibuprofen API market was $573 million. It is estimated to grow by $645 million with a CAGR of 2–3 % by 2023.

● North America, with its matured market, is the 2nd largest manufacturer of Ibuprofen.

2) Europe has a strong buying power and lacks manufacturing capability, resulting in mostly importing Ibuprofen from other regions.

3) China and India are major suppliers for Ibuprofen with low buying capability.

4) India supplies 40 % of the Ibuprofen API to Europe, and the U.S. gets 90% of its Ibuprofen demands met by importing from China.

5) The Ibuprofen API market is a consolidated market with the leading manufacturers accounting for around 90 percent of the market value.

6) COVID-19 has had an adverse impact on the Ibuprofen market. China has elevated the price of Ibuprofen by 22% due to the pandemic.

7) As India is dependent on China for raw materials, the pandemic has led India to decrease its dependency on China.

8) India has adequate production of the API and is currently exporting to the developed nations, like the U.S., the UK, Italy, Germany, and Canada, with their high demand for Ibuprofen.

9) India has enough stock to manufacture Ibuprofen tablets for the next three months.

❖ **Identification of the most widely prescribed drug from a selected class (consumption report) by approaching pharmacy stores, company representatives, and pharma companies web portal.**

➢ **Consumption report (united states 2013 - 2020).**

☐ **Top drug rank #38 (9).**

Estimated number of prescription in the United States (2020)	1,65,33,209.
Estimated number of patients in the United States (2020).	8,89,6,328.

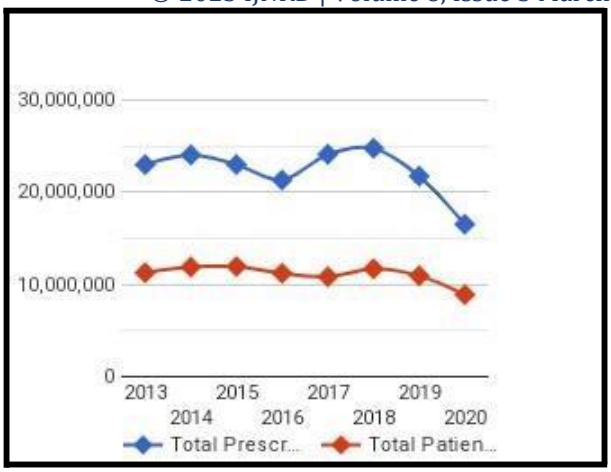
☐ **Average total drug cost :-**

Per prescription	$10.07.
Per day of therapy	$0.61/day.

☐ **Average out of pocket cost :-**

Per prescription	$2.80.
Per day of therapy	$0.19.

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



➢ **Rank of Top Drugs Over Time:-**

Year	Rank	Change
2013	33	↑5
2014	31	↑2
2015	31	0
2016	34	↓3
2017	27	↑7
2018	26	↑1
2019	29	↓3
2020	38	↓9

➢ **Drug cost over time (2013- 2020) :-** ☐ **Cost Per Prescription Fill:**

Average cost per filled prescription regardless of how many days of therapy the prescription is filled for (e.g. 10 days, 30 days, 90 days, etc.)

☐ **Cost per Day of Therapy:**

The average cost per prescription fill divided by the days of therapy. For example, a 10-day antibiotic course costing $30 would be $3 per day. Similarly, a 30-day supply of an oral antihypertensive costing $30 would be $1 per day.

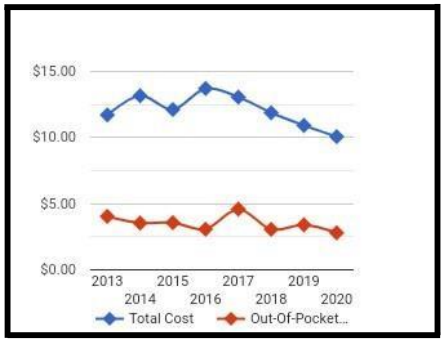
☐ **Total cost:**

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

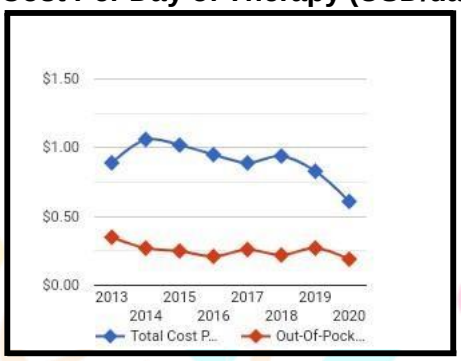
☐ **Out-of-pocket cost:**

The average payment made by the patient which may include deductibles, coinsurance, copayments, or the cash price paid without insurance coverage.

➢ **Cost Per Prescription Fill (USD)**



➢ **Cost Per Day of Therapy (USD/day)**

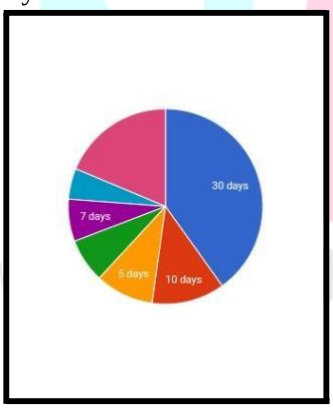


➢ **Distribution of Dispensed Dosage Forms (2020):-**

Dosage form	Strength	%of dispensed product
Tablet / capsule	800mg	62.5%
Tablet / capsule	600mg	27.7%
Other unspecified or misc	-	9.8%

➢ **Distribution of Days Supplied (2020):-**

"Days supply" is defined as the number of days that a prescription should last. For example, a prescription of 60 tablets that is taken twice daily has a day supply of 30 days.



➢ **FDA approval information :-**

Established pharmacologic class	NSAID
Initial FDA approval date	Prior to January 1. 1982
First FDA applicant	Discn
First dosage form	Tablet (oral).

❖ **Identification of adverse effects of a selected drug**.

➢ Identification of adverse effects of a selected drug using different search engines [Medscape, drugs, rxlist].

☐ **Before taking this medicine :-**

You should not use ibuprofen if allergic to it, or if you have ever asthma attack of severe allergic after taking aspirin of an NSAID

- Ask a doctor or pharmacist if this medicine is safe to use if you have ever had:
- heart disease, high blood pressure, high cholesterol, diabetes, o if you smoke ● a heart attack stroke of blood clot.
- stomach ulcers or bleeding.
- liver or kidney disease. ● asthma.

☐ **Ask a doctor before using this medicine if you are pregnant or breastfeeding**:-

- If you are pregnant you should not take ibuprofen unless your doctor tells you to.
- Taking an NSAID during the last 20 weeks of pregnancy can cause serious heart or kidney problems in the unborn baby and possible complications with your pregnancy.
- Do not give ibuprofen to a child younger than 6 month old without the advice of a doctor .

☐ **Side effect motrin [ibuprofen]** ● Stomach pain. ● Constipation.

- Diarrhoea. ● Bloating. ● Heartburn ● Nausea.
- Vomiting.
- Dizziness.
- Headache.
- Nervousness.
- Skin itching or rash .
- Blurred vision. ● Ringing in the ears ● Skin rashes.

☐ **If I overdose** :-

- Seek emergency medical attention or call the poison help line at 1800-2221222.
- Overdose symptoms may include - nausea vomiting, stomach pain, drowsiness, black or bloody stools, coughing up blood, shallow , breathing, fainting or coma

☐ **What to avoid :-**

- Ask a doctor or pharmacist before using other medicines for pain fever , swelling, or cold/flu symptoms.
- They may contain ingredient similar to ibuprofen (such as aspirin , ketoprofen, naproxen).

Adverse Drug Reaction (ADR) Monitoring Form :-

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

Sr .no	Indian pharmacopoeia commission	For AMC/NCC Use only
	Report type clinical follow up -	AMC report no -
		World wide unique no -
A	Patient information	12-Relevent test/laboratory date with date
1	Patient initial	13-Relevent medical history e.g.- pregnancy allergy
2	Age at time event	
3	M-. F-. Other -	
a	Weigh. Kg/s	
B	Suspect adverse reactions	14- serious relations
5-	Date of started	• Death. • Congited
6-	Date of recovery	• Life threatening
7-	D described reaction problem	• Disability
		15- outcome • Recover • Rp covering

Suspected medication:-

Sr .n	Name Brand generic	Manufacture ers	Batch no	Exp date	Dose used	Freque ncy	Route used	Indicati on casualt y assess ment
1								
2								
3								

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

Additional information :-	D. Reporter details 16- name and professional address- Pin-. E-mail - Help no- (with STD code)Occupation -. Sign- . 17- date this report -

❑Patient interview :-

Interview of patients for under -standing & identification of Adr.

- Hospital name:- Matoshri Ayurvedic hospital & research center.
- Patient name :- Thube Akshay .
- Age :- 20.
- Gender:- male.
- Disease:- headache & back pain (painkiller) ● Drug :- besiflam.
- Drug ADR: o Nausea. o Anxiety.
- o Swelling.
  ○ Ulceration of stomach.
- Dosage :- besiflam tablet. ○ Ibuprofen 400 mg.
- o Paracetamol 325 mg.
- Routes of administration:○ Oral route of administration.

Reference :-

1)https://www.slideshare.net/drashutoshtiwari
2) Pharmacovigilance textbook by dr.sb bhise & mrs.m.s bhise . page no 4.1- 4.5.
3)The textbook of pharmaceutical medicine 4th edition page no -249-250 by john p Griffin.
4)A pharmacy practice book by dr.rajesh Kumar nema & dr.rajendra s batpana page no 31.3 & 31.9
5)Pharmacovigilance: Needs and Objectives 6)
7)https://www.aiims.edu/aiims/departments_17_5_16/pharmacology/pvpi/pvpi.htm#:~:text=The%20purpose%20of%20the%20Pharmacovigilance,healthcare%20professionals%20and% 20the%20public.
8)http://www.pharmabiz.com/PrintArticle.aspx?aid=63422&sid=18
9)https://www.slideshare.net/priyasri8/ibuprofen-93001853
10)https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3353548/
11)https://www.researchgate.net/publication/323186470_Preclinical_Study_of_Ibuprofen_Loaded_Transnasal_Mucoadhesive_Microemulsion_for_Neuroprotective_Effect_in_MPTP_Mic e_Model
12)https://www.tandfonline.com/doi/abs/10.3109/01480545.2011.630670?journalCode=idct2

13)https://europepmc.org/article/med/12723741
14)https://pubmed.ncbi.nlm.nih.gov/19949916/
15)https://www.beroeinc.com/category-intelligence/ibuprofen-market/
16)https://clincalc.com/DrugStats/Drugs/Ibuprofen
17)RxList - The Internet Drug Index for prescription drug information …
18)Latest Medical News, Clinical Trials, Guidelines - Today on Medscape
19)Drugs.com | Prescription Drug Information, Interactions & Side Effects
20)https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdfdocuments/Consumer_Secti on_PDFs/ADRRF_2.pdf