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A SYSTEMIC REVIEW OF PHARMACOVIGILANCE SYSTEM IN SAFE DRUG TREATMENT: INDOMETHACIN

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ABSTRACT

Pharmacovigilance is the track to select safe drug during treatments. pharmacovigilance provide information about safe and appropriate drug during drug treatment. The adverse drug reaction are main component of pharmacovigilance. Adverse drug reaction became major problem in the developing countries. By the World Health organisation pharmacovigilance is science and activity relating to the detection, assessment, understanding & Prevention of adverse effect or any other drug related problems. pharmacovigilance play very import role in healthcare system by monitoring the adverse effects of drug. This review article summerized objective, types and methods use in Pharmacovigilance with their Pharmacovigilance program of India and also study of Indomethacin, their adverce effect by Pharmacovigilance.

Indomethacin is Non Steroidal Anti Inflammatory Drug use in rheumatoid arthritis ,patent ductus arteriosis, Osteoarthritis. The machanism of Indomethacin is by inhibiting synthesis of Prostaglandin. This article describe side effects , adverse effects of Indomethacine and provide instructions for the safe use of drug.

Keyworld: Indomethacine Safety,Spontaneous Adverse Drug Reporting.

I. INTRODUCTION

Pharmacovigilance -: It is science & activities melting to the detection assessment understanding & prevention of adverse effect or any other problems Possible drug related problems.

pharmacovigilance also known as drug safety

It plays a vita in ensuring that doctors, together with the Patient, have enough. information to make decision when it comes to Choosing a drug for treatment.

In Some countries adverse drug reaction rank among the top 10 leading Causes OF mortality.

In order to prevent or to reduce harm to patients and thus improve public health mechanism for evacuating of monitoring the safety of medicines in clinical use are vital.

Objectives -:

- Improvement of patient care and safety in relation to use of medicine with medical & paramedical intervent" remains to be an parameters.
- The main objective of pharmacovigilance involve the efficacy of drug by monitoring their adverse effect profile for many years from the lab to Pharmacy; tracking any drastic effects of drugs improving public health and safety in relation to the use of medicine; encouraging the safe rational and cause effective use of drugs; promoting understanding education of and clinical training in PV and effective communication to generic public.
- In addition providing information to consumers, practitioners and regulators on the effective use of drug along with the designing program and produce for collection and analysing reports from patients.

Components of PV -:

components of PV includes

1) Adverse even case management
2) Aggregate report management
3) safety signal management.
4) Risk management.
5) Individual Case reporting.

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Adverse event case management -:

When a safety registry is created as a condition of regulatory approval, a data safety monitoring (DSMB) Board is data monitoring committee (PMC) OrAdjudication Committee with may be or established with primary role of reviewing the data the generated by registry.

Generally discusses directly with regulatory authorities such as FDA. These authorities involved in design and protocol for post approval studies.

The management of AE reporting should be clearly specified in registry protocol including explanation of the roles, responsibilities, processes and method for handling AE Reportby various registry.

FPA proposed rule for safety, reporting requirement for Human drug & Biologics products suggest that the responsible point of the Contact for PDA Should provided for all expedited Periadiac AE reports and preferably this individucus, should licensed Physician.

Updated PV regulations issued by European Medicines Agency are expected to be implanted in July 2012

Aggregate report managements -: Aggregate reporting is process of review the cumulative safety information from a wide range of sources , on a periodic basis & submits finding to regulators worlwide.

These reports focus not so much on individual Cases but rather on overview asserment of Safety profile & risk benefit evaluation of APR & Serious adverse event & pregnancy reports.

Types of Aggregating reports -:

a) pre-marketing report.

- IND annual report

-Clinical study reports.

- Development safety update reports
- Annual safety reports.

1) Post-marketing reports

- periodic Benefit risk Evolution report.

-periodic adverse drug experience report

- NDA and ANDA annual reports
- Addendum to clinical overviews.

3) safety signal management -:

The safety signal management process is based on the examination Of individual Case safety reports (ICSR) aggregate data from active surveillance system

The following steps of signal management process -: Signal detection

Signal validation Signal prioritization Signal assessment

Recommendation for action Exchange of information

4) Risk managements -:

The management of single risk can be Considered four steps -

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

These focuses on activities that should be developed in the risk minimisation plan to be applied more to biopharmaceuticals and more specifically to biosimilar.

- The biopharmaceuticals often exhibit Safety such as immunotoxicity that lead to loss efficacy.

Different steps of risk management -:

- Identify risk
- Understand the risk

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- Communicate the risk Act to reduce mistake

Types of pharmacovigilance -:

1) passive surveillance - :

passive surveillance involve the usage of spontaneous adverse event reports voluntarily send by healthcare professionals or patients to marketing authorisation holder or regulatory

- The identify of the reporter remains anonymous but patient related details like country, age, gender & pre-existing, comorbiditier Can be recovered from the reporting forms.

2) Active Surveillance -:

This method aims to monitor certain specific drug related adverse event and no of certain adverse ADR entirely through a pre-planned process.

3) Coherrant monitoring -:

In this method the survilance Study is planned prior to begining the treatment with the medications Adverse event of target drug or the event of target drug associated with one Or more medicine take with that drug are monitored.

4) Targated clinical investigations -:

This kinds of investigations are performed to identify & characterize the adverse reaction related to drug among Special population like people with some genetic disorder ,preganant Women & older people.

Constitution & objective of PVPI-:

The CDSCO directorate General of Health services under the aggies of Ministry of Health & Family welfare, Govt. of India in association Indian pharmacopoeial commission Gaziabad is initiating a nation-wide pharmacovigilance Programme for protecting health of Patient by promising drug safety.

The PVPI was on 14 July 2010 started by GOVT OF India objective -:

- To create nation wide system for Patient safety reporting.
- To identify & analyze the (ADR) from reported new signal cases.
- To analyse the benefit-risk ratio of marketed medications.
- To generate the evidence based information on safety of medicines.
- To support regulatory agencies in decision making process on use of medication.
- To communicate safety information on use of medicine.
- To Collaborate with other national Centres for the data exchange of information and data mangement.
- TO provide training & consultancy support to other national PV canters located across globe

Functions -:

1) Identification and analysis of new adverse reaction signal from case report
2) provision of WHO database as refference source for signal strengthning
3) Information exchange between WHO & National centres by email information exchange system.
4) Running training courses in Pv.
5) Publication of periodical news letter in Pharmacovigilance

List of national Adverse drug monitoring Centres & their functions **-:**

1) parameter of pharmacology Medical clg. Gowahan,Assam.
2) Institute of pharmacology Madras. Medical College Chennai.
3) Department of pharmacolgy SAIMS medical Collage Indore - ujjain
4) Dept. of P`cology JIPMER Pondicherry.
5) Department of clinical pharmacy JSS medical clg. Hospital. karnataka.
6) Dept. of clinical & Expt. p'cology school of Tropical medicine, chirraranjan Avenu, kolkata.
7) pept. of •Clinical prolong seth, G's medi- 0 Cal clg. & KEM Hospital parel Mumbai.
8) Dept. of p'cology, PGIMER chandigarh
9) pept of Pharmacology R.Akar medical clg. kolkata.

10) Dept. of etg. p'cology Enbsbsp Therape- utics & Toxicology Govt medical clg. Bakshi Magar Jammu

The Precilinical studies are conducted as per guidelines of schedule Y of drug in India.The schedule Y contains set of regulation and guidelines for permission of development (preclinical

/clinical) i.e import ,manufacturing of new drug and also marketing of new drug in India. These guidelines amended in 2005 New Drug (IND) to conduct the studies which contain mainly introduction ,chemical and pharmaceutical information, animal pharmacology and toxicology and clinical trials.

Pre- clinical studies are conducted on the animals .After the synthesizing /identifying a prospective compound, this test on animal for Pharmacovigilance effects profile. The used experimental animals are smaller -mouse, rat, guinea pig, rabbit and larger animal -Cat ,dog monkey.

In evalution progress the unfavourable entity rejected for each step ,only few out of thousands reach to stage when administration to human.

Following types of test are performed -:

- Screening test :-The test for detection of particular pharmacodynamic activity in presence or absence. Eg.Analgesic
- Test on isolated organs, bacterial cultures:-Preliminary test for detection of specific activity. Eg.Antibacterial activity.
- Test on animal models of human diseases:-The kindled seizures in rat ,genetically hypertensive rat ,experimental tuberculosis in mouse ,alloxane induced diabetes in rat or dog etc.
- Confirmatory test and analogous activities:-Elaborate test which confirmed and characterize the activity other related activities .Eg.Antipyretics and Anti inflammatory activities are tested in analgesic .
- Systemic pharmacology:-The detection of primary action of drug also mechanism of action including additional mechanism.
- Quantative test:-The test perform for dose response relationship ,maximal effect and comparative potency /efficacy with the drug .
- Toxicity test :- The main aim of this test us determine safety of the compound in the two animals species or more in which rodent and non rodent both animals are use .By both routes Oral and parenteral. Also Formulated Acute toxicity ,chronic toxicity, subacute toxicity, reproductive toxicity and teratogenicity.

CLINICAL TRIALS

Clinical trials is medical research involving human participants .for standard design ,ethics, conduct, monitoring ,recording, auditing&anlysis of data are laid down in the form of Good Clinical Practices (GLP) guidelines by International Conference In Harmonization (ICH).

Following are phases of clinical trials -: Phase 0:-Micro-dosing study

The optimal pharmacokinetic on healthy volunteers .These are alarmed FDA and cost cutting approach in drug development many drugs fail in clinical trials due to substance.

Phase1:-Human pharmacology and safety.

Used healthy volunteers are 20 to100.Determination of metabolic and pharmacodynamical effect in human. The drug administered by qualified clinical pharmacologist mostly healthy volunteers . The main aim of these phase is determination of safety.

Phase 2:-Therapeutics explanation of dose ranging .

The use of Individual within target disease . The used patients are 100-300.Establishment of the rapeutic efficacy, dose range. Factor to identifying is checking for efficacy. Phase 3:-Therapeutic confirmation.

Safety and tolerability study by FDA NDA covered marketing permission. Used individuals and targeted diseases gastric patient and pregnant women .The no. candidates are use 300- 1000.Main object of this is assessment of safety,tolerability,possible drug interactions . Main factor to identifying is both efficacy and safety calculate.

Phase 4 :-Post marketing surveillance .

The no. of objective are used 1000-3000.The used individual are age groups ,targeted disease well aged .main

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objective of the phase is monitor safety in large people. The factors of identification is safety and efficacy within large people.

Good Clinical Practice

ICH-International Conference On Harmonization

II. OBJECTIVES

To provides overview of history of good laboratory practices.

1) Recognize the implications of non compliance.
2) Review the positive and negative case study.
3) Emphases importance of international Conference on harmonization good clinical practice compliance when conducting clinical trials.
4) Provide protection to the patient.
5) Avoid trial duplication for medicinal product containing new.

SCOPE OF GCP -:

Good clinical practice used an laboratories ; test are done on biological specimen diagnosis patient care disease cannolo..

- Histopathology
- Haematology and blood bank.
- Molecular pathology and
- Molecules biology.
- serology.
- Micro-biological.

PROTOCOL AND AMENDMENT COMPOUND -:

- Assessment of efficacy.
- Assessment of safety.
- Statistics
- Data handling and management.
- Quality control and quality assurance.
- Finance

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- Insurance
- Publication policy.
- Evolution.
- Supplementary and appendices.

CLINICAL TRIALS APPLICATION PROCESS:-

A Clinical Trials Application (CTA) is the application/submission to the competent National regulatory affairs(NRA) for authorization to conduct a clinical trial a specific Country.

Process:-

Clinical trials application submission

1) Validation of submitted documents.
2) Requesting to complete the submitted dose.
3) Evolution of the whole clinical trial application.
4) Deficiency requirements request on data information missing on submitted file.
5) Evolution report or recommendation.
6) Study food and drug authority.
7) Clinical trial application approved.

SELECTION OF DRUG

Indomethacin:-

Discovery and development -:

• Discover in 1963 and approve for use in US by FDA in 1965

• ThisisNSAID drugchemicalnameis1-(P-chlorobenzoyl) 25methoxy 2- methylindol 3- acetic acid .

- it is indole derivative class drug.
- nonselectivecocksanybetterinhibitormainlyinhibitsynthesisofPGandThromboxinvia.

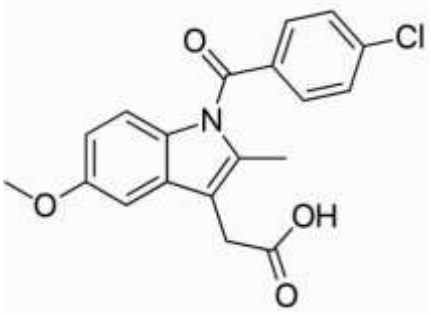
Inhibiting Arachidonic acid. Brand name -: Indosin, Tivorbex Generic Name -: Indomethacin

Uses -:

1) In patent ductus arteriosis of premature infant
2) Rheumatoid arthritis.
3) Osteoarthritis
4) Acute gouty arthritis
5) Postoperative ocular information. Dosage form-:

- Oral - (capsule)
- In PDA – Intravenous
- In POI -Topical

Chemical formula -: C19H16ClNO4 Molecular weight -: 357.7 mol Structure -:



Mechanism of Action - :

The NSAID drug Indomethacine is of non-selective & reversible inhibitor of Cyclooxygenase [Cox] enzyme / Prostaglandin G/H synthase.

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Two Isomer of COX enzyme 1.COX 1 -:

present in body tissues & help in synthesis of PG & Thromboxine A2.

2. COX 2 -: Is express in response to injury of inflammation cox2 catalayse the conversion of Arachidonic acid to PGG2 to PGH2 is converted to PGE2 and PGI2.

Decrease in PGE2 involved in mediating inflammation action, pain and fever.

Indomethacin know to inhibition of both COX1 and COX2. Indomethacin binds to enzyme active and prevents the intereaction between enzymes and substrate i. e Arachidonic acid Inhibition Phospholipase A2 the enzyme responsible for releasing Arachidonic acid from Phospholipid.

The exact machanism of indomethacin in including closure of patent ductus arteriosius not fully understand.

Inhibit PG synthesis At the birth of baby closed the tension of O2 increases after birth. PGE1 mediated opposite effect to O2. PGE1 dilate ductus arteriosus through smooth muscle relaxation & prevent the closure of ductus arteriosus by preventing synthesis of prostaglandin.

Side effect -:

1) back or leg pain
2) breast enlargement
3) stomach cramp
4) Burning
5) Diarrhoea
6) Indigestion
7) Nausea
8) vomiting Toxicology **-:**

√ Drag disease interaction -:

- Indomethacin + Asthma -: Bronchoconstriction
- Indomethacin in urticaria -: pain

√ Drug-Drug interaction -:

- Ibuprofen +Indomethacin -: Ulcer , Inflammation
- Warfarin + Indomethacin -: Decrease B. P

√ Drug + interaction-:

- Indomethacin + High protein /High fat food -: decrease absoption IND.

√ contraindication -: contraindicated after heart Surgery (like bypass) Design and conduct of observation of studies -:

- Experimental approach -:

Rat treated actually by Intravenous or chronically with subcutaneous injection of vehicle, indomethacin or INDO-PC using three related protocol.

We then evaluated foll. Properties of parenteral administired test drug .

1. GI Toxicity (Luminal and faecal bb;intestinal adhesion)
2. Bioavailability (plasma Indomethacin)
3. Therapeutic efficacy

In rats with adjuvant induced joint inflammation. Animal methods -:

Approval for all protocol call obtained from institutional animal welfare committee which follow guideline & is accredited by us public aid service male sprague Dawley rats 200-250g use in studies

Animal were maintained on 12 hours light /dark cycle with food and water provided libitum. Drag formulation -:

Indomethacin was obtained from sigma chemical co. It was dissolved in 1.25% Sodium bicarbonate with low heat (40°c) the pH was 7.4

It was sterilized by filtration (0.22 microns) prior to dosing. Acute efficacy -:

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To evaluate therapeutic of indomethacin, both the analgesic response to pressure applied to an inflamed paw and ability to inhibit PG synthetic. All CFA injected animal had the same level of sensitivity to a pressure stimulus, with the pain pressure threshold being consistently lower than baseline values measured prior to CFA.

At 30 min receiving a single iv dose either IND sod. Bicarbonate, increase in pressure threshold of IND. Animal, give analgesic effects or efficacy. The level of PGE2 in inflamed paw synovial fluid was elevated in saline treated CFA rate.

To confirm that bioavailability of IND was similar IND. CFA-complete freund adjuvant.

Identification of most widely prescribed drug from a selected class (consumption report)by approaching pharmacy stores ,company representative and Pharma Companies web portal.

Indomethacin is a non steroidal anti inflammatory (NSAIDS)class drug which are used in treatment of acute pain ,rheumatoid arthritis ,osteoarthritis ,ankylosing Spondylitis ,bursitis , gouty Arthritis and also in a patent ductus arteriosis.

Administration or consumption of indomethacine-:Indomethacin is available in the oral dosage form are tablet form, extended release capsule, immediate release capsule formulation.

The immediate release capsule range started from 25 mg to 50 mg and extended release capsule are 75 mg.The oral suspension of 25 mg per 5 ml is available in market.

The Indomethacin is also given intravenous route in the patent ductus arteriosus IV injection 1mg base per vial or rectal suppositories 50 mg.

At the lowest dose for shorter duration to avoid potential side effects. AcutePain -:

In acute paint the orally indomethacin give 20mg or 40 mg thrice or twice in a day. #Rheumatoid Arthritis Ankylosing Sponditis and Osteoarthritis #

In rheumatoid arthritis the 25 mg dose given two or three times in a dayorally or rectal route as immediate release formulation.The dose should be increased weekly up to 25 mg to the maximum dose 200mg per day .

At the Bedtime give 100 mg for patients with arthritis. Also 75mg extened relesed capsule administered. The maximum recommended dose for extended releases capsule dosage from is 150mg

In Bursitis Treatment -;

In Bursitis the orally Indomethacin administered immediate release formulations 75-150 mg. If given rectal route three /four divided dose .The 75-150mg extended release formulations administered orally in one or two doses.

In Gouty Arthritis-:

In gouty Arthritis the Indomethacine oral or rectal route 50 mg thrice in a day. specific population -;

1) Renal impairment-:In Renal impairment no adjustment of dosage form. Not given at stages of renal impairment.
2) Hepatic impairment-:Indomethacin can give with caution for patient with hepatic impairment.
3) Preganat Impairment-:It is FDA pregnancy category C medicine and use should be avoided.
4) Breast feeding Women -: At low level dosethe indomethacin should used in treatment of breastfeeding wom

THE MEDICINE MANUFACTURED BY

1) Brand Name : Indo

Manufacturers : Shalina Laboratories Pvt. Ltd. Type : Capsule

2) Brand Name : Artid-SR Manufacturers : Digmedi (P) Ltd. Type : Capsule
3) Brand Name : Indoc – SR Manufacturers : Octane Biotech Pvt. Ltd Type : Tablet
4) Brand Name : Indocap

Manufacturers : Jagsonpal Pharmaceuticals Ltd. Type : Tablet

5) Brand Name : Indocid SR Manufacturers : Cipla Limited Type : Capsule
5) Brand Name : Artid-SR Manufacturers : Digmedi (P) Ltd. Type : Capsule
6) Brand Name : Indmecin

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Manufacturers : Surmount Labs Pvt Ltd (Sterkem Pharma Pvt Ltd) Type : Drops

7) Brand Name : Indoflam Manufacturers : Recon Healthcare Ltd. Type : Capsule

8) Brand Name : Inocin

Manufacturers : Bombay Tablet Mfg. Co. Pvt. Ltd.

Type : Tablet

9) Brand Name : Methadocin Manufacturers : Sunways (India) Pvt. Ltd. Type : Drops

10)Brand Name : Recticin

Manufacturers : Bliss Chemicals Pharma India Ltd. Type : Suppository

11)Brand Name :DUCTACLOSE Manufacturer:Genex Pharma .Ltd Type:Injection .

Identification of adverse Effects:-

Effect of selected drugs.

Identification of adverse effect of selected drug using different search engines (example medscape.com And drug.com, rxlist.com etc)

Adverse drug reaction of Indomethacin-:

1) On CNS -:

-Depression

- Confusion

-Tinnitus –

Headache

2) On llung -: Asthma -Bronchoconstriction -Aspirin inducedasthma

3) 3)On Skin-: Rash

4) On kidney-: Secondary to decrease blood perfusion through theglomeruli Renal Failure

5) On GIT -: Peptic ulcer Duodenal ulcer

6) On Liver -: Hepatotoxicity elevated liver function tests

7) Heart failure

8) Hypertension

9) Sodium retention

10) Cardiovascular problems.

Adverse drug reaction monitoring form Preparation of ADR monitoring form as per guideline given by AMCS Example Indian pharmacopia Commission

Process of induction of AMCS undbeginer PVPIspeech

1. MCI approved Medical College or institute and hospitals
2. furnishing the letter of intent
3. Duly forwarded by head of the institution
4. NCC – PvPI
5. Examining the stability by NCC

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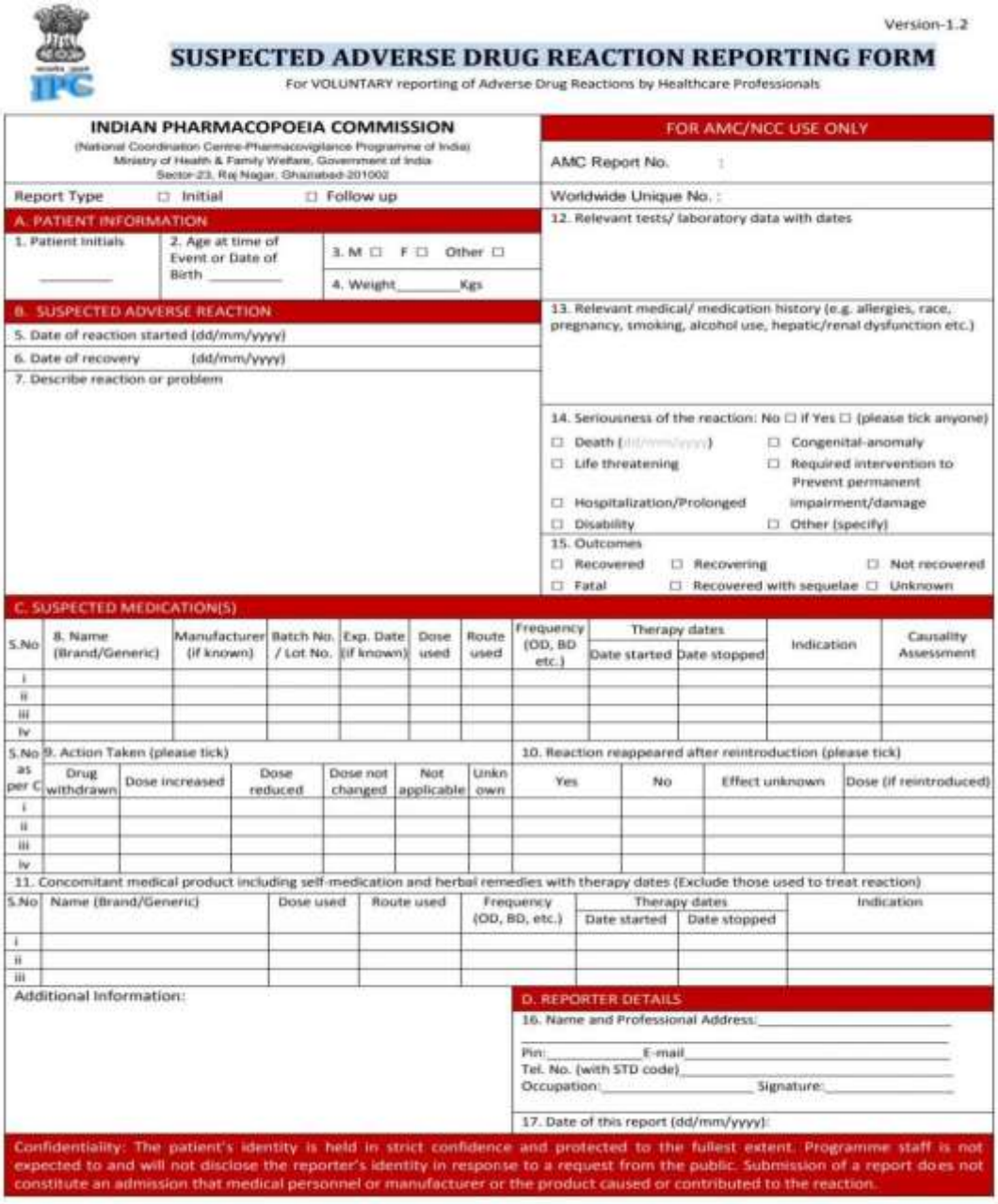

Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

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

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

Report Type ☐ Initial ☐ Follow up

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

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

12. Relevant tests/ laboratory data with dates
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 ☐ Other (specify)
☐ Disability
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: Date started	Therapy dates: Date stopped	Indication	Causality Assessment
i											
ii											
iii											
iv											

S.No as per C	9. Action Taken (please tick): Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	10. Reaction reappeared after reintroduction (please tick): 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: Date started	Therapy dates: Date stopped	Indication
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.

6. NCC excepting as AMCS under communicating to Following

A. Ministry of Health and family welfare Government of India

III. CONCLUSION

pharmacovigilance play an important role in the meeting the challenges poused by Increasing range and potency of medicine. when adverse effect and toxicity are appear are shown, special event unknown there essential Reported and analysed detected and their significance are the communicated with patient or public to give knowledge about to reduce the adverse effect and toxicity. The harmful can be minimised or reduce by ensuring the quality good, safety , efficacy and also rational use of Indomethacin. To achieve this result need to give knowledge about drug indomethacin drug use their management to public. This review article supported the adverse effect , toxicity and also safety, efficacy of the indomethacin.

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