



Study Of Pharmacovigilance Related Drug Isoniazid

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Abstract

Pharmacovigilance deals with safety & monitoring of drugs for the purpose of detection of frequency of adverse drug reaction to improve patients' healthcare & safety. Adverse drug reactions have been a large-scale problem in developing countries which brings pharmacovigilance as a major field in drug manufacturing & development. Pharmacovigilance is aimed at increasing reporting rates and minimizing adverse drug reactions.

As pharmacovigilance is concerned with toxicology studies of drugs this study deals with the account of isoniazid (referred as first line anti tubercular drug) This review is concerned with data collected about toxicology & account of isoniazid.

Keywords: -

Pharmacovigilance, toxicology, isoniazid, adverse drug reaction, clinical trials

Clinical Research.

➤ Clinical trials :

- Clinical trials are a response. Studies performed in people that are aimed at evaluating medical, surgical or beta Vioxal interventions.
- Clinical trials are a type of research that studies new tests and treatments, and evaluates their effect on humans.. health outcomes.
- People volunteer to take clinical trials to test medical intervention including drugs, cell and, other, biological products, surgical procedures, radiological procedure devices, behavioral treatment and preventive care.
- Clinical trials are carefully designed reviewed and completed, and need to be approved before they can, stare people or all, ages take part in clinical trials, including children

➤ Types of clinical trials.

- Clinical trials should be conducted and analyzed, according to sound, scientific principle, with due regard to clinical consideration, in under, to achieve, the trial The objective
- Bob foul trials must to reported, fully and objectively and result must be ass visible to those who need them

→ Phases of clinical trials

1. .Phase 0:-

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

2. Phase 1:-

- Phase 1 trials are the first studies of an investigational new drug in humans.
- Phase 1 trials may be conducted in individuals who have the disease the drug is intended to treat.
- The Phase-1 has a duration of 1 month to 12 months.
- Phase 1 generally involves between 20 to 30 participant

3. Phase 2:-

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

4. Phase 3:-

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

5. Phase 4:-

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

➤ Pre -clinical phase

- Exide Details of non-clinical / pre-Clinical studies are discussed under, ICH, Ms guideline the details are motioned, below. De
- It includes safety pharmacology, studies reported, dose toxicity studies, toxicokinetic and non-clinical pharmacokinetic studies.
- Animal safety studies, and Human clinical trials, should be designed, to Cand, ethical.

➤ Phases of preclinical trials

● Safety pharmacology :-

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

● Toxicokinetic & Pharmacokinetic studies:-

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

● Acute toxicity studies:-

- This information has been obtained From single dose toxicity studies in two mammation species using both the clinical and parenteral route of administration.
- This available to phase III clinical trials for higher risks overdose eg. Depression, pain, dementia.

● Respected Dose toxicity:

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

● Local Tolerance studies:-

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

● Genotoxicity studies:-

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

● Carcinogenicity studies:-

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

● Reproductive toxicity:-

- It is Should be conducted as appropriate as the population that is to be exposed. There are four categories: women not of child bearing, women of child bearing in pregnant women.

● Other toxicity:-

- Non-clinical study eg. identify potential biomarkers

➤ **function of Drug controller General of India (DCGI) and central drug standard control organization (CDSCO)**

● **DCGI**

1. Preparation and maintenance of material reference standard. Minorities to bring about the unit the informant of the and
2. Cosmetic Act. Training of drug Analysts dependent by state • drug controlled laboratories and other institution

● **CDSCO**

1. Approval of new drug and clinical trials.
2. import Registration and licensing
3. license approving Blooded Bank, lops, Vaccine, r-DNA product and same medical derivative.
4. Testing new drug
5. grant of test license For export personal kknnot

➤ **Type In combination new drug (TWD) New drug application, (NDA) and Activate New Drug Application (ANDA).**

● **Investigational new during Application (IND)**

- a. To identify and contact information of and are phase of trials Sponsor and one phase of trials.
- b. A commitment that in IRB coil be Represent for initial and Continuing review of trials.
- c. The name of the doug list of ingredient and it's dosage and route of administration
- d. The objective planned deviation of the proposed clinical trials.

● **New drug Application (NDA)**

- a. The identify and contact information of the sponsor and the phase of the trials. A commitment that an IRB will be responsible for initial and continuing review of The trials.
- b. The name of the drug is a list of its active ingredient and its dosage and route of Administration. The objective and planned duration of the proposed clinical trials. Identities and qualifications of all investigators
- c. Submission of an NDA is the form step asking the FDA to consider a drug for marketing approval. The FDA has 60 days to decide whether to file it so it can be reviewed.

● **Abbreviated, new drug Application, (ANDA) -**

- a. An abbreviated new drug application ANDA contains data which is submitted to FDA for the review and potentially approval of a generic drug product. Once approved an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand name drug it references.
- b. This act also premises brand name companies to apply for exclusive patient rights to cover their new drug for up to 5 year.

Goods clinical practice (GCP)

- **ICH GCP:-**

- In the middle part of the last century drug development, experiences several event t that gave weight to greater harmonization within Initially and then International In theUSA terrible mistake in the form
- ICH - Good clinical practice
- Quality data + ethics + GCP (Good clinical practice)

- **The Good clinical practice cover**

1. Design
2. Performance
3. Monitoring
4. Auditing
5. Analysis
6. Reporting.

- **Objective**

- a. To provide an overview of history of good clinical practice (international conference harmonization)
- b. To emphasize importance of ICH CACP Compliance when conducting clinical trial
- c. To recognise implication of non- compliance
- d. To review positive and negative case studies
- e. Protect and patient
- f. Avoid trials duplication
- g. Theatrical requirement for medicinal product containing new

- **Scope of GCP**

- Good clinical laboratory should be used by all laboratories where test are done on biological diagnosis patient cover diseases control
- Micro- biological and serology
- Hematology and blood boating
- Molecular biology and molecular pathology
- Clinical pathology
- Histopathology

- **Key change in2019 new drug and clinical trial rules**

In new rule 2019 such research has been defined to include studies on basic applied and operational research or clinical research designed primarily to increase scientific knowledge about diseases and condition (physico - sociobehavioral) their and cause evolving strategy health promotion Prevention amelioration diseases rehabilitation does not include (T study type include)

- In Vitro diagnosis (. INDS) performance testing for research
- New surgical intervention
- Assisted reproductive technology (PRT)
- epidemiological and non- interventional study of old drug
- There type studies should be approved ethics committees constituted under pulele registered under rule 17 with cosco office as ethics committees for Biomedical and health research

➤ **Academic clinical trial:-**

- New rule 2019 described academic clinical trial as clinical trial of drug already approved for certain claim and initiated by investigator academic research institution for new indication or new route of administration or new dose or new dosage form .
- Some important point for academic clinical trial include :-
 - Only for approved drug
 - CT initiated investigator academic or, research authority (CLR) and CIA must respond in indication new route new dose or new dosage
 - EC can seek clarity from central licensing authority (CLA) and (LA) respond in 30 days or deemed that no approval needed medical management and compensation application as per ICMR guideline biomedical research on human participants academic CTS required conduct accordance with CT protocol approval Ec Guideline for biomedical research human participant

➤ **Ethics committee (ECS) :-**

1. In addition the 2019 CT rules established a separate registration and monitoring system for ECS that oversee bio- medical and health research studies .
2. PCR notice 15 Sept 2019 and chapter IV of the 2019 CT rules any institutions and organization that plan to conduct bio - medical and health research involving human participant is not required to have EC to review overcast conduct such research before study

● **EC Composition :-**

Pursuant to the 2019 CT rules and ICMR guideline institutional independent EC should be multidisciplinary multi sectional representing mixed gender ,age, composition. As per 2019 CT rules ICMR guideline composition should involve following:-

1. Chairperson from outside of the institute
2. One (1) to two (2) basic medical scientist preferably one (1) pharmacologist
3. One (1) to two (2) clinical from various institution
4. Legal expert or retired judge
5. One (1) social scientist / representative non- government voluntary agents
6. One (1) philosopher / ethics / theologian
7. One (1) lay person from community
8. Member secretary

➤ **Phase IV & post marketing studies (PMC)**

Previously there was ambiguity define requirements phase IV & PMC new rule 2019 was to differentiate requirements conducting phase IV CT & Post marketing surveillance for new drug.

● **New rule 2019 phase IV studies**

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

● **Post marketing surveillance studies :-**

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

● Orphan Drug registration

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

● Post -trial access

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

● Other significant update

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

Concept of Pharmacovigilance

● Definition

pharmacovigilance is the science and activity relating to the detection assessment , understanding and prevention of adverse effects or any other medicinal, urine related problems for patient safety .

● Objective

- Improvement of patient charcoal safety in relation to the use of medicines with medical and paramedical important parameter
- The main objective of pharmacovigilance involves exhibiting the efficacy of drugs by monitoring their adverse effect profile for many years from the lab to the pharmacy tracking and drastic effect of drug improving public health and safety.relation to the use of medicines encouraging the safety radiation and cost effective use of drug.
- Promotion understanding education and clinical training in pharmacovigilance to the generic public
- In addition providing information consumers particitieness and regulators on the effect use of drug along with designing programs and procedure for collecting and analyzing report to the object of pharmacovigilance

● Type

There are four important 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 use of spontaneous adverse event reports volunteered by healthcare professionals or patients to the marketing Authorization regulatory authority. The data related to the derivation are collected in a central or regional database.

2. Active surveillance

This method aims to monitor certain specific drug-related events and seeks to ascertain the number of ADRs entering through a pre-planned process. It is commonly known as toxicity monitoring or safety monitoring.

3. Cohort event monitoring:

-In this method, the study is planned prior to beginning the treatment with the medication. A group of people are exposed to a drug for a defined period, and activity is followed up during treatment. Adverse effects of the target drug or the event 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 reaction related to a drug among special populations like people with the same genetic disorder, pregnant women, and older people.

Constitutional object of pharmacovigilance of India.

The purpose of the PV program of India is to collect and analyze data to arrive at an opinion to recommend regulatory intervention besides communicating risks to healthcare professionals.

● PVPI

The central drug standard control organization (CDSCO) directorate general of population health services under the aegis of ministers of health and family welfare Government of India, in collaboration with the department of pharmacology, All India Institute of Medical Science (AIIMS), New Delhi, launched the nation-wide PV program for protecting the health of the patient by ensuring drug safety.

● Objective

- To monitor ADR in India population
- To create awareness among healthcare professionals about the importance of ADR.
- To monitor benefit-risk profile to monitor
- Generate independent evidence-based recommendations on the safety of medicines
- Support the classes for formulating safety-related regulatory decisions for medicines.
- Communicate findings with all key stakeholders
- Create a national center of excellence at par with global drug safety monitoring standards.

List of national adverse drug monitoring center and their functions:-**● National coordinating center (NCC).**

1. Department of pharmacology all india institute of medical science New Delhi.

Co-ordinators- Dr Y.K.Gupta National coordinator.

● ADR monitoring center (AMC).

1. Department of pharmacology and ADS and NHSBSP: therapeutics and toxicology GOVT medical College Bakshi nagar Jammu.

Co-ordinators- Dr Vishal tandon.

2. Department pharmacology PGIMER Chandigarh

Co-ordinators- Dr Bakshi medhi

3. Department of pharmacology RG kar medical College Kolkata

Co-ordinators- Dr Anjan Adhikari.

4. Department of pharmacology body hoarding medical College New Delhi.

Co-ordinators- Dr H.S Rehan

5. Department of clinical pharmacology Saint GS medical College of KEM hospital Mumbai

Co-ordinators- Dr. Urmila Matte .

6. Department of clinical Exp pharmacology school of hospital medicine Chandigarh.

Co-ordinators- Dr. Santanu tripati

7. Department of pharmacology JIPMER Pondicherry.

Co-ordinators- Dr. C. Adithan.

8. Department of clinical pharmacy TSI medical College hospital Karnataka.

Co-ordinators- Dr. Prashant. G

9. Department of pharmacology medical College Guwahati.

Co-ordinators- Dr. Mangala. lonkar

10. Institute of pharmacology Madras medical College Chennai.

Co-ordinators- Dr. R. Nandani.

11. Department of pharmacology GSVM medical College Swaroop Nagar.

Co-ordinators- Dr. S.P. Singh.

12. Department of pharmacology s a i m s medical College Indore

Co-ordinators- Dr. Chnaya .goyal .

13. Department of pharmacology pandit Bhagwat Dayal Sharma post graduate institute of medical science Rohtak Haryana.

Co-ordinators- Dr. M.C Gupta.

14. Department of pharmacology Dayanand medical college Ludhiana and Punjab.

Co-ordinators- Dr. Sandeep Kasuhal.

15. Department of clinical pharmacology Shri I Krishna of medical science Srinagar Jammu and Kashmir.

Co-ordinators- Dr. Z.A. Wafal.

16. Himalayan Institute of medical Dehradun Uttarakhand.

Co-ordinators- Dr. D.C Dhasmana.

17. Department of pharmacology Santosh medical university Santosh Nagar Ghaziabad.

Co-ordinators- Dr V.C Chopra .

18. Department of pharmacology s m s medical College Jaipur.

Co-ordinators- Dr. Mukul. Mathur.

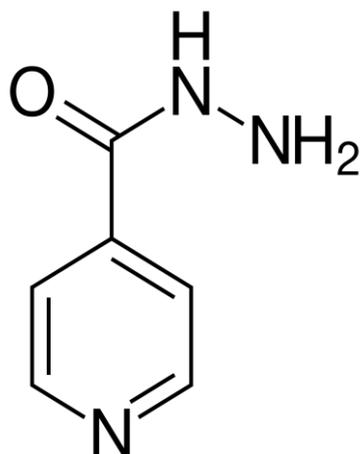
19. Department of clinical pharmacology Christian medical College vellore Tamil Nadu.

Co-ordinators- Dr. Sujith. Chandy.

Selection of Drug Class

Drug : Isoniazid

- **Introduction** : Isoniazid is an antibiotic used to treat mycobacterial infections most commonly use in combination with other antimycobacterial agents for the treatment of active or latent tuberculosis. It is bactericidal for growing bacteria and bacteriostatic. It is a prodrug and it gives their action by inhibiting the synthesis of mycolic acid which decrease the synthesis of cell wall and bacteria kills or inhibits the growth.
- **Drug Class** : Antimycobacterials
- **Chemical formula** : $C_6H_7N_3O$
- **Molecular weight** : 137.139
- **Structure** :



➤ **Synonyms :**

4-pyridine carbohydrazide

Isoniazid

Isoniazida

Isonicotinic acid hydrazide

Isonicotinic hydrazide

Isonicotinohydrazide

Isonicotinylhydrazine

Isonicotinsäurehydrazid

Isonicotinylhydrazine

➤ **Brand name :**

Isonarif

Isotamine

Isotamine B

Rifamate

Rifater

Mybasan

Hucozid

Iscotin

➤ **Route of administration :**

Isoniazid is normally taken orally but may be administered Intramuscularly Or Intravenously to critically ill patients

➤ **Dosing :**

1. **For oral dosage forms (tablets, syrup) :**

For treatment of tuberculosis:

1. **Adults and teenagers :** 300 mg once a day; or 15 mg per kg (6.8 mg per pound) of body weight, up to 900 mg, two times a week or three times a week, depending on the schedule your doctor chooses for you.
2. **Children :** Dose is based on body weight. The usual dose is 10 to 20 mg per kg (4.5 to 9.1 mg per pound) of body weight, up to 300 mg, once a day; or 20 to 40 mg per kg (9.1 to 18.2 mg per pound) of body weight, up to 900 mg, two times a week or three times a week, depending on the schedule your doctor chooses for you.

For injection dosage form:

For treatment of tuberculosis:

- **Adults and teenagers** : 300 mg once a day; or 15 mg per kg (6.8 mg per pound) of body weight, up to 900 mg, two times a week or three times a week,
- **Children** : Dose is based on body weight. The usual dose is 10 to 20 mg per kg of body weight, up to 300 mg, once a day; or 20 to 40 mg per kg of body weight, up to 900 mg, two times a week or three times a week

➤ **Storage :**

Store isoniazid **oral solution** at room temperature, 68°F to 77°F (20°C to 25°C).

Store isoniazid **tablets** at 68°F to 77°F (20°C to 25°C) and protect them from moisture and light. Keep isoniazid in the container that it came in and keep the container tightly closed

➤ **Discovery/History :**

Isoniazid is a synthetic antimicrobial and One of the most important first - line drugs used in the treatment of tuberculosis Since it was introduced in the therapy. in 1952.

It was first synthesized in 1912 but its discovery as an antitubercular agent was first reported simultaneously and independently was first reported in the early 1950s by researchers from Hoffmann La Roche, ER Squibb and son in the United States of America and from Bayer in Germany. After, its discovery as Anti-TB drug isoniazid was introduced in the therapeutic regimen for TB treatment in 1952. (Marshall et al, 1952: Medical Research Council 1954

➤ **Development :**

Isoniazid is available in tablet form at a the Concentration of 100 mg In addition, the drug is also used in combination with rifampicin. In soft capsules at two different concentration 100 mg + 150 mg and 200 mg + 300 mg

Respectively. According to WHO drug quality control comprises the set of procedures undertaken to ensure the identity and purity of a particular pharmaceutical. These produces may be performed mainly through chromatographic methods eg. HPLC, GC, TLC Several analytical techniques are used to determine drug quality such as infrared spectroscopy, UV, MS Therefore the Pharmaceutical analysis specifically the development and application of analytical method plays an important role to ensure the quality of medicines and also quantification of specific drug in biological sample

➤ **Pre- Clinical Research :**

Isoniazid is the hydrazide of isonicotinic acid used to treat M. tuberculosis infections.

Rats:

In studies with LPS (lipopolysaccharide) does that elicit a mild inflammation (increased cytokines and COX2 expression), no tissue injury ensues. However, when these doses are coadministered with aflatoxin B or a potentially hepatotoxic drug, the threshold for toxicity is lowered more than 10-fold. Both biliary injury (increased GGT) and hepatocellular necrosis (increased ALT) are demonstrated. In some studies, animals not only demonstrated increased sensitivity to toxins with LPS but also showed a change in tissue target for toxicity. This appears to depend on the agent and the exposure paradigm, thus mimicking the human idiosyncratic reactions. Isonicotinic acid hydrazide (isoniazid) at 150 mg/kg ip to rats elicited an increased in total plasma lipids, triglycerides, cholesterol, phospholipids and free fatty acids for <30 hours. post dosing. This response was followed by an increase in these same parameters in liver with a decrease in adipose tissue. This implies increased mobilization of depot fat into the liver.

- **Carcinogenicity studies in animals**

IARC evaluated several carcinogenicity studies, in mice, rats and hamsters, and noted positive findings in mice after exposure to isoniazid via different routes.^{1,2} The animal studies evaluated by IARC are summarized in Annex E.

Additional studies do not involve the inhalatory route and have a number of methodological limitations, such as use of partially hepatectomies animals, application of a single dose level and/or inclusion of insufficient numbers of animals.

- **Oral administration**

- **Studies with rats**

Gershbein and Rao administered a diet containing 0.030% isoniazid to 13 young adult male Sprague-Dawley rats for 87 weeks.²¹ Two rats died during the course of the study. At necropsy, chronic nephritis was observed in two of the survivors, of which one displayed panniculitis. Tumors were absent throughout the gastrointestinal tract of the animals treated with isoniazid. Also no subcutaneous tumors were noted. Clinical chemistry revealed no remarkable differences compared to the control animals that received a plain diet.

In this study, also the effect of isoniazid in the diet on 1,2-dimethylhydrazine induced tumorigenesis was studied. Ten male weanling rats were fed a plain and an isoniazid-containing diet, respectively, for 15 days, after which 1,2-dimethylhydrazine was injected subcutaneously at a dosage of 9.0 mg/kg bw once per week for 7 weeks, then twice weekly for a total of 23 injections. Colon adenocarcinomas occurred in 80-100% of the animals (22 in the plain diet group; 28 in the isoniazid group).

- **Conclusion**

Several types of tumors have been reported in different strains of mice.

Although these studies show limitations and the results are not consistent, these findings cannot be ignored. The Committee concludes that there is limited evidence of carcinogenicity in animals

➤ **Clinical Research :**

- ❖ **Study Description :**

Isoniazid (INH) is a drug commonly used to treat TB worldwide. Sometimes, the bacteria that cause TB can become resistant to INH. Resistance means that bacteria have adapted to a drug and are able to live in the presence of the drug. When TB becomes resistant to INH, INH does not work as well at fighting the bacteria. This study will treat people with INH-resistant TB with different doses of INH to see if INH can still fight the bacteria if we just increase the dose. We will compare how well the drug works at higher doses for participants who have resistant TB to how well the drug works at regular doses for participants who have TB that is not resistant. The study will also compare the safety and tolerability of the different doses of INH. Tolerability is how well people can put up with the side effects of a drug. Using increased doses of INH to treat TB that is resistant to INH is experimental and has not been approved by regulatory authorities. While there is some evidence that this approach will work, this has not yet been proven.

This study will be done in two stages. Stage 1 is a pilot study to determine the feasibility of enrolling enough participants into Stage 2, the larger stage of this study. If Stage 1 is successful, then Stage 2 will begin.

Condition or disease	Intervention/treatment	Phase
Tuberculosis	Drug: Isoniazid Dietary Supplement: Vitamin B6	Early Phase 1

❖ Study Design

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	282 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Primary Purpose:	Treatment
Official Title	The Early Bactericidal Activity of High-Dose or Standard-Dose Isoniazid Among Adult Participants With Isoniazid-Resistant or Drug-Sensitive Tuberculosis
Actual Study Start Date :	August 13, 2014
Actual Primary Completion Date :	September 22, 2021
Actual Study Completion Date :	October 6, 2021

❖ Arms and Interventions

Arm	Intervention/treatment
<p><u>Experimental: Group 1:</u> Participants with a TB strain that has an inhA mutation Participants who meet Step 2 entry criteria will be randomized 1:1:1 to receive the following treatments for 7 days:</p> <p>5 mg cohort: Isoniazid 5 mg/kg daily plus vitamin B6 \geq25 mg daily 10 mg cohort: Isoniazid 10 mg/kg daily plus vitamin B6 \geq25 mg daily 15 mg cohort: Isoniazid 15 mg/kg daily plus vitamin B6 \geq25 mg daily</p>	<p>Drug: Isoniazid INH is available in 100 mg tablets. INH will be administered orally daily in the morning on an empty stomach. Doses of INH will be given according to the weight bands. Other Name: INH</p> <p>Dietary Supplement: Vitamin B6 Vitamin B6 will be administered at \geq 25 mg daily and will be obtained locally for use by study participants.</p>

<p><u>Experimental: Group 2:</u> Participants with TB without inhA nor katG mutations Participants who meet Step 2 entry criteria will receive Isoniazid 5 mg/kg daily plus vitamin B6 ≥ 25 mg daily for 7 days</p>	<p>Drug: Isoniazid INH is available in 100 mg tablets. INH will be administered orally daily in the morning on an empty stomach. Doses of INH will be given according to the weight bands. Other Name: INH Dietary Supplement: Vitamin B6 Vitamin B6 will be administered at ≥ 25 mg daily and will be obtained locally for use by study participants.</p>
<p><u>Experimental: Group 3:</u> Participants with an MTB isolate with a katG mutation with or without an inhA mutation Participants with an M. tuberculosis isolate with a katG mutation with or without an inhA mutation who meet Step 2 entry criteria will be randomized to receive either Isoniazid 15 mg/kg or 20 mg/kg daily, plus vitamin B6 ≥ 25 mg daily for 7 days.</p>	<p>Drug: Isoniazid INH is available in 100 mg tablets. INH will be administered orally daily in the morning on an empty stomach. Doses of INH will be given according to the weight bands. Other Name: INH Dietary Supplement: Vitamin B6 Vitamin B6 will be administered at ≥ 25 mg daily and will be obtained locally for use by study participants.</p>

❖ **Eligibility Criteria :**

Ages Eligible for Study: 18 Years to 65 Years (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

➤ **Clinically significant of isoniazid :**

The most important factor determining the speed with which isoniazid is eliminated from the body is the rate of its acetylation in the liver. There are large differences between individuals in the rates at which isoniazid is acetylated. Over 98% of subjects can be clearly characterized as being either rapid or slow acetylators. Among the many satisfactory procedures for determining the acetylator phenotype of subjects, the simple sulfamethazine method is probably the most convenient. The proportions of rapid acetylators among different populations vary from about 40% among those of European and South Indian descent to over 85% among Japanese and Eskimos. The isoniazid acetylator phenotype of tuberculosis patients treated with isoniazid-containing regimens is without prognostic significance when treatment is given daily and only of doubtful importance when weak twice-weekly regimens are employed. However if treatment is given on a once-weekly basis, the response of rapid acetylators is generally much less satisfactory than that of slow acetylators. Since isoniazid is eliminated from the body predominantly by metabolism its clearance is not greatly diminished in the event of renal failure.

➤ **Safety monitoring of isoniazid :**

- patients given isoniazid should be carefully monitored and interviewed at monthly intervals
- Serum transaminase conc becomes elevated In about 10-20% of patients.
- patients should be instructed to report immediately any of the prodromal symptoms of hepatitis such as fatigue, weakness, malaise, anorexia, nausea, vomiting - If these symptoms appear hepatic damage are detected
- Isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage

➤ **Pharmacokinetics :**

❖ **Absorption :**

- Isoniazid is usually administered orally, but if the patient is critically ill, the drug can be delivered intramuscularly or intravenously as slow 5-min bolus in 25 ml of normal saline, however undergo significant first pass metabolism. Absorption and bioavailability are reduced when isoniazid is administered with food

❖ **Distribution :**

- Diffuses readily into cerebrospinal, pleural and ascitic fluid tissue, organs, saliva, sputum in feces placental barriers readily into all body fluid and tissue.

❖ **Metabolism :**

- Isoniazid is metabolized in liver by acetylation
- Rate of acetylation of isoniazide is under genetic control
- In some people are rapid acetylators rapid acetylators are more likely to develop hepatotoxicity
- slow acetylators are liable to neuropathy

❖ **Elimination :**

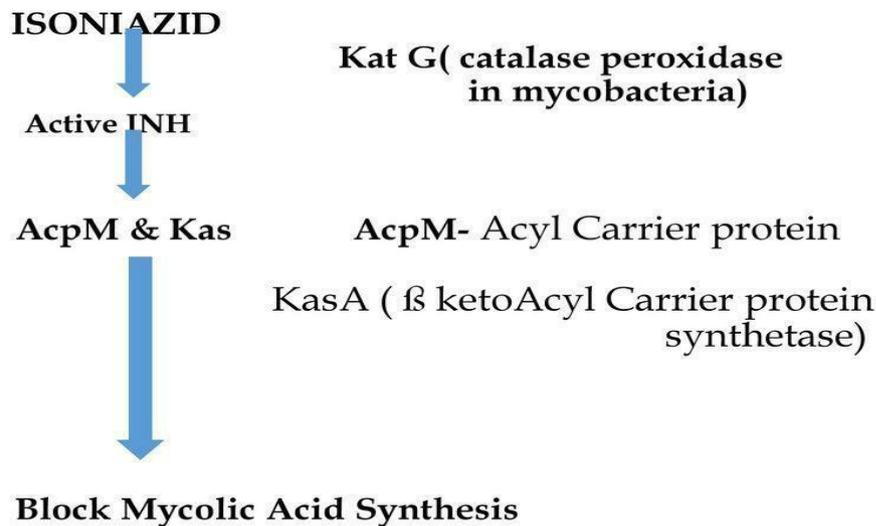
- urinary excretion is primary elimination route (approx 50 to 70% in 24 h)

➤ **Pharmacodynamic :**

Isoniazid is a bactericidal agent active against organisms of the genus Mycobacterium, specifically M. tuberculosis, M. bovis and M. kansasii. It is a highly specific agent, ineffective against other microorganisms. Isoniazid is bactericidal when mycobacteria grow rapidly and bacteriostatic when they grow slowly.

❖ **Mechanism of action**

Isoniazid is a prodrug and must be activated by bacterial catalase. Specifically, activation is associated with reduction of the mycobacterial ferric KatG catalase-peroxidase by hydrazine and reaction with oxygen to form an oxy ferrous enzyme complex. Once activated, isoniazid inhibits the synthesis of mycolic acids, an essential component of the bacterial cell wall. At therapeutic levels isoniazid is bactericidal against actively growing intracellular and extracellular Mycobacterium tuberculosis organisms. Specifically isoniazid inhibits InhA, the enoyl reductase from Mycobacterium tuberculosis, by forming a covalent adduct with the NAD cofactor. It is the INH-NAD adduct that acts as a slow, tight-binding competitive inhibitor of InhA.



➤ Adverse reaction of isoniazid :

The most frequent reactions are those affecting the nervous system and the liver.

- **Nervous System Reactions**

Peripheral neuropathy is the most common toxic effect. It is dose-related, occurs most often in the malnourished and in those predisposed to neuritis (e.g., alcoholics and diabetics) and is usually preceded by paresthesias of the feet and hands. The incidence is higher in “slow inactivators”.

- **Other neurotoxic effects**

which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis.

- **Hepatic Reactions**

Elevated serum transaminase (SGOT; SGPT), bilirubinemia, bilirubinuria, jaundice and occasionally severe and sometimes fatal hepatitis. The common prodromal symptoms of hepatitis are anorexia, nausea, vomiting, fatigue, malaise and weakness.

- **Gastrointestinal Reactions**

Nausea, vomiting, epigastric distress, and pancreatitis.

- **Hematologic Reactions**

Agranulocytosis; hemolytic, sideroblastic or aplastic anemia, thrombocytopenia; and eosinophilia.

- **Hypersensitivity Reactions**

Fever, skin eruptions (morbilliform, maculopapular, purpuric or exfoliative), lymphadenopathy, vasculitis, toxic epidermal necrolysis, and drug reaction with eosinophilia syndrome (DRESS).

- **Metabolic And Endocrine Reactions**

Pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis and gynecomastia.

- **Miscellaneous Reactions**

Rheumatic and systemic lupus erythematosus-like syndrome.

➤ **Contraindications :**

- Isoniazid is contraindicated in patients who develop severe hypersensitivity reactions, including drug induced hepatitis previous isoniazid-associated hepatic injury severe adverse reactions to isoniazid such
 - fever
 - chills
 - arthritis
 - acute liver disease of any etiology.
 - Pregnant women

➤ **Drug interaction of isoniazid :**

● **Acetaminophen**

A report of severe acetaminophen toxicity was reported in a patient receiving Isoniazid. It is believed that the toxicity may have resulted from a previously unrecognized interaction between isoniazid and acetaminophen and a molecular basis for this interaction has been proposed. However, current evidence suggests that isoniazid does induce P-450IIE1, a mixed-function oxidase enzyme that appears to generate the toxic metabolites, in the liver.

● **Carbamazepine**

Carbamazepine levels should be determined prior to concurrent administration with isoniazid, signs and symptoms of carbamazepine toxicity should be monitored closely and appropriate dosage adjustment of the anticonvulsant should be made

● **Ketoconazole**

Potential interaction of Ketoconazole and Isoniazid may exist. When Ketoconazole is given in combination with isoniazid and rifampin the AUC of ketoconazole is decreased by as much as 88 percent after 5 months of concurrent Isoniazid and Rifampin therapy

● **Phenytoin**

Isoniazid may increase serum levels of phenytoin. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant should be made

● **Theophylline**

A recent study has shown that concomitant administration of isoniazid and theophylline may cause elevated plasma levels of theophylline and in some instances a slight decrease in the elimination of isoniazid. Since the therapeutic range of theophylline is narrow, theophylline serum levels should be monitored closely and appropriate dosage adjustments of theophylline should be made

● **Valproate**

A recent case study has shown a possible increase in the plasma level of valproate when co-administered with isoniazid. Plasma valproate concentration should be monitored when isoniazid and valproate are coadministered and appropriate dosage adjustments of valproate should be made

➤ **Carcinogenesis and Mutagenesis :**

Isoniazid has been shown to induce pulmonary tumors in a number of strains of mice. Isoniazid has not been shown to be carcinogenic in humans. (Note: a diagnosis of mesothelioma in a child with prenatal exposure to isoniazid and no other apparent risk factors has been reported). Isoniazid has been found to be weakly mutagenic in strains TA 100 and TA 1535 of Salmonella typhimurium (Ames assay) without metabolic activation.

➤ Food interaction :

Isoniazid should not be administered with food. Studies have shown that the bioavailability of isoniazid is reduced significantly when administered with food. Because isoniazid has some monoamine oxidase inhibiting activity, an interaction with tyramine-containing foods (**cheese, red wine,sausages and salami, fava beans, sauerkraut, soy sauce, beer,)** may occur. Diamine oxidase may also be inhibited, causing exaggerated response (e.g., headache, sweating, palpitations, flushing,hypotension) to foods containing histamine (**e.g., skipjack, tuna, other tropical fish**).

➤ Precautions of isoniazid :

General

Use of isoniazid should be carefully monitored in the following:

1. Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis.
2. Patients with active chronic liver disease or severe renal dysfunction.
3. Age greater than 35.
4. Concurrent use of any chronically administered medication.
5. History of previous discontinuation of isoniazid.
6. Existence of peripheral neuropathy or conditions predisposing to neuropathy.
7. Pregnancy.
8. Injection drug use.
9. Women belonging to minority groups, particularly in the postpartum period.
10. HIV seropositive patients.

➤ Toxicity :

❖ Acute toxicity

Acute INH overdose predominantly involves the brain and may cause prolonged seizures, anion gap metabolic acidosis, and coma. Note the following:

- Patients who are affected may present with active tonic-clonic seizures and thus may be unable to give a history of INH use; this often makes rapid identification of acute INH toxicity difficult without third-party input.
- The amount ingested is also often difficult to ascertain, making accurate antidote (pyridoxine) dosing challenging.
- Clinical manifestations may appear as early as 30 minutes after ingestion.

❖ Chronic toxicity

INH hepatotoxicity presents a difficult management problem, for several reasons, including the following:

- Patients who are affected often are taking other potentially hepatotoxic drugs, such as pyrazinamide or protease inhibitors; this makes it difficult to determine which drug is causing the liver damage.

- Most cases of INH hepatotoxicity are mild and commonly resolve despite continued therapy with INH; however, a small number of adult patients taking INH develop severe hepatitis that may progress to liver failure and death if the drug is not stopped promptly.
- Lack of effective alternative drugs often necessitates that INH be continued
- despite low-grade hepatotoxicity.
- Patients who are severely affected may have few symptoms until potentially lethal liver damage has occurred.

Selection of drug class for pharmacovigilance study using different criteria (commercial availability, selling if drug)

- Isoniazid also known as isonicotinic acid hydrazide (INH)
- It is an antibiotics used for the treatment of tuberculosis

❖ Brand name of isoniazid

- Hydra
- Hyzyda
- Isovit
- Laniazid
- Nydrazid
- Rimifon
- Stanozide
- Isonarif
- Isotamine
- Rifamate
- Rifates

❖ Other name

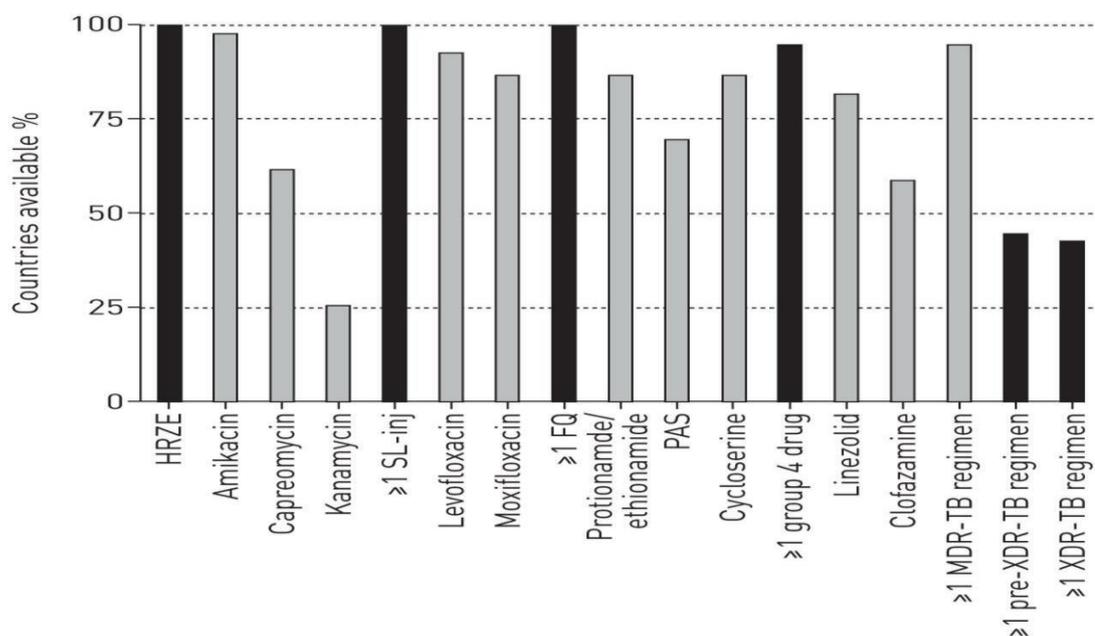
- Isonicotinic acid hydrazide
- Isonicotinyl hydrazine
- INH
- INAH
- INHA

❖ Synonym of isoniazid :

- 4-pyridin carbohydrazide
- Isonicotinic hydrazide
- Isonicotinohydrazide
- Isonicotinylhydrazine
- **Drug class** : Anti-Tuberculosis

❖ Availability :

Availability was reported as the number and percentage of countries in which individual drugs were available during the data collection period. We defined preferred and alternative treatment regimens for drug-sensitive TB, multidrug-resistant (MDR)-TB (resistant to isoniazid and rifampicin), pre-extensively drug-resistant (XDR)-TB (resistant to at least one fluoroquinolone or a second-line injectable in addition to isoniazid and rifampicin), and XDR-TB (resistant to at least one fluoroquinolone, second-line injectable, isoniazid and rifampicin) All of the current 28 member states of the European Union were included in the analysis, except for Malta. We also included Serbia, Former Yugoslav Republic of Macedonia (FYROM) and Montenegro (candidate member states); as well as Norway, Switzerland, Republic of Moldova, Ukraine, Bosnia and Herzegovina, Albania and Belarus. The data from Kosovo were excluded because all drugs were reported to be free-of-charge at the point of use.



➤ Selling of drug :

All first-line drugs (isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E)) were available in all countries surveyed. 17 of the 37 countries indicated the use of FDC in first-line treatment. For only two countries, we needed to use the cost of FDCs to estimate the cost of individual drugs. Amikacin

was available in all counties except Bulgaria. Capreomycin was available in 22 (59%) countries, while kanamycin was available in only nine (24%) countries. Moxifloxacin and levofloxacin were available in 34 (92%) and 32 (86%) countries, respectively. All countries had at least one second-line injectable (SL-inj) and one fluoroquinolone (FQ) available. Prothionamide/ethionamide (Pto/Eto) and cycloserine/terizidone (Cs/Trd) are essential in the preferred treatment regimen for MDR-TB, while para-aminosalicylic acid (PAS) is essential in the alternative MDR-TB regimen. These drugs were available in 31 (86%), 32 (86%) and 26 (70%) countries, respectively. Three countries did not have any of these drugs available (Albania, Serbia, Greece), while another two countries (Bosnia and Herzegovina, Slovakia) had just one of these drugs available.

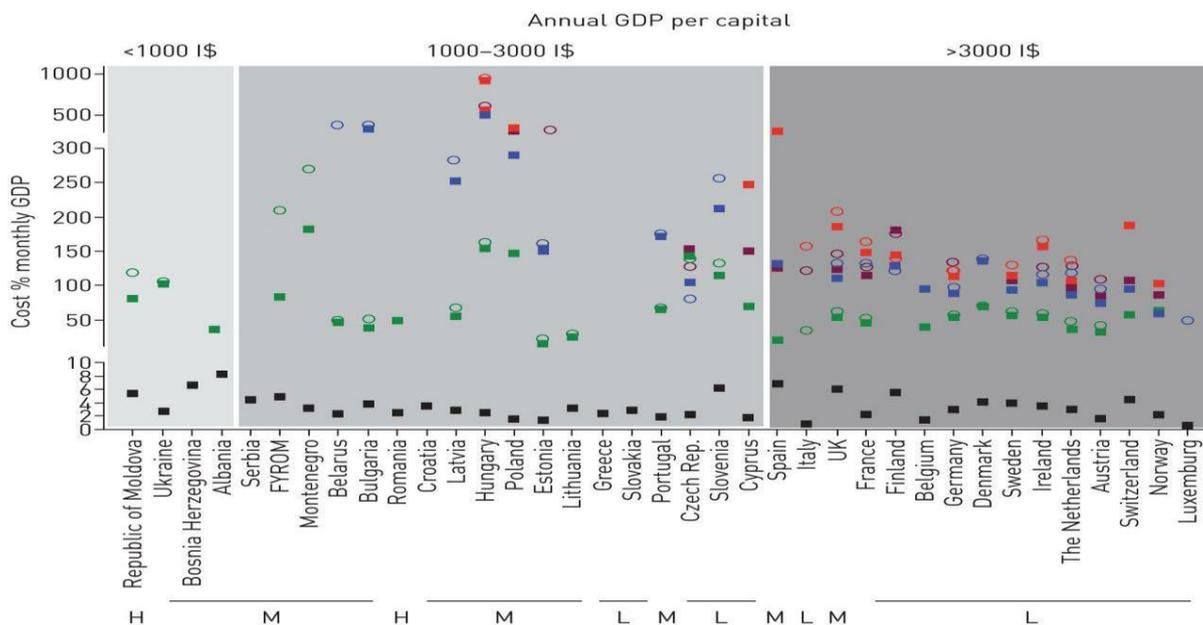
Average price per day treatment for individual drugs

Treatment group	Drug name (route)	Dose mg·day ⁻¹	Cost			
			Euro		I\$	
			Min	Max	Min	Max
Group 1	Isoniazid (orally)	300	0.40	3.12	0.01	4.52
	Rifampicin (orally)	600	0.09	3.79	0.25	3.40
	Ethambutol (orally)	1200	0.07	4.72	0.17	5.76
	Pyrazinamide (orally)	200	0.06	3.63	0.14	3.60
Group 2	Streptomycin (i.v./intramuscular)	1000	0.12	21.96	0.33	26.76
	Amikacin (i.v.)	750	0.60	131.8	1.81	141.82
	Capreomycin (i.v.)	1000	2.67	172.5	4.67	218.82
	Kanamycin (i.v.)	1000	0.17	15.98	0.52	30.73
Group 3	Levofloxacin (orally)	1000	0.15	26.88	0.32	40.21
	Moxifloxacin (orally)	400	1.10	14.06	1.41	16.63

Identification of most widely prescribed drug from a selected class (consumption report) by approaching pharmacy store, company representative, and pharma companies web portal

➤ Consumption report :

In all countries, the cost of a month's first-line regimen remained below 8.5% of a month's GDP in 2012. In seven countries, the cost was more than 5% of a month's GDP per capita, of which five were in Eastern or Southern Europe (Republic of Moldova (5.5%), Slovenia (6.3%), Bosnia and Herzegovina (6.7%), Spain (6.8%), Albania (8.3%)) and two were in Northern or Western Europe (Finland (5.7%), UK (6.0%)). In Italy and Luxembourg, the cost of a month's course first-line regimen was below 1% of a month's GDP per capita but for different reasons: in Italy, the price of the first-line regimen was relatively inexpensive, while Luxemburg has the highest GDP of the countries surveyed. The percentage of monthly GDP per capita represented by a month's treatment with the preferred MDR-TB regimen remained below 30% in just three countries, while for 13 countries it was above 60%, of which for seven countries above 100% (Ukraine (101%) Slovenia (114%) Finland (124%) Poland (146%) Czech Republic (147%) Hungary (155%) Montenegro (182%)



Identification of adverse effects of a selected drug

● Nervous System Reactions

- toxic encephalopathy
- optic neuritis
- atrophy
- memory impairment
- toxic psychosis.

- **Hepatic Reactions**

- anorexia
- nausea
- vomiting
- fatigue
- malaise
- weakness

- **Gastrointestinal Reactions**

- Nausea
- vomiting,
- epigastric distress
- pancreatitis.

- **Hematologic Reactions**

- Agranulocytosis
- hemolytic
- sideroblastic or aplastic anemia
- thrombocytopenia
- eosinophilia.

- **Hypersensitivity Reactions**

- Fever
- skin eruptions (morbilliform, maculopapular, purpuric or exfoliative)
- lymphadenopathy
- vasculitis
- toxic epidermal necrolysis

- **Metabolic and Endocrine Reactions**

- Pyridoxine deficiency
- pellagra
- hyperglycemia
- metabolic acidosis
- gynecomastia.

- **Miscellaneous Reactions**

- Rheumatic syndrome
- systemic lupus erythematosus

Black Box Warnings

Severe and sometimes fatal hepatitis may occur within the first 3 months of treatment and many months after treatment. Risk is related to age and increased with daily alcohol consumption.

Patients should be instructed about signs and symptoms of hepatitis.

❖ Before Using

In to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This is a decision you and your doctor will make. For this medicine, the following should be considered:

- **Allergies**

Tell your doctor if you have ever had any unusual or allergic reaction to this medicine or any other medicines. Also tell your health care professional if you have any other types of allergies, such as to foods, dyes, preservatives, or animals. For non-prescription products, read the label or package ingredients carefully.

- **Pediatric**

Isoniazid can cause serious side effects in any patient. Therefore, it is especially important that you discuss with the child's doctor the good that this medicine may do as well as the risks of using it.

- **Geriatric**

Hepatitis may be especially likely to occur in patients over 50 years of age, who are usually more sensitive than younger adults to the effects of isoniazid.

- **Breastfeeding**

Studies in women suggest that this medication poses minimal risk to the infant when used during breastfeeding.

Adverse Drug Reaction (ADR) Monitoring Form

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



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				
Report Type <input type="checkbox"/> Initial <input type="checkbox"/> Follow up							AMC Report No. : _____				
A. PATIENT INFORMATION							Worldwide Unique No. : _____				
1. Patient Initials _____		2. Age at time of Event or Date of Birth _____		3. M <input type="checkbox"/> F <input type="checkbox"/> Other <input type="checkbox"/>		12. Relevant tests/ laboratory data with dates					
				4. Weight _____Kgs							
B. SUSPECTED ADVERSE REACTION							13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)				
5. Date of reaction started (dd/mm/yyyy) _____											
6. Date of recovery (dd/mm/yyyy) _____							14. Seriousness of the reaction: No <input type="checkbox"/> if Yes <input type="checkbox"/> (please tick anyone) <input type="checkbox"/> Death (dd/mm/yyyy) <input type="checkbox"/> Congenital-anomaly <input type="checkbox"/> Life threatening <input type="checkbox"/> Required intervention to Prevent permanent impairment/damage <input type="checkbox"/> Hospitalization/Prolonged <input type="checkbox"/> Disability <input type="checkbox"/> Other (specify) _____				
7. Describe reaction or problem _____											
C. SUSPECTED MEDICATION(S)							15. Outcomes <input type="checkbox"/> Recovered <input type="checkbox"/> Recovering <input type="checkbox"/> Not recovered <input type="checkbox"/> Fatal <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Unknown				
9. Action Taken (please tick)											
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.											

Patient interview :-

Interview of patients for under -standing & identification of ADR

- Hospital name:- matoshri Ayurvedic hospital & research center.
- Patient name :-
- Age :- .
- Gender:-
- Disease:- Anti-Tuberculosis
- Drug :- isoniazid

- **Drug ADR:-**

- Loss of appetite
- Nausea
- Vomiting
- Stomach pain
- Weakness
- Dizziness
- Slurred speech
- Lethargy

- **Dosage :-**

- **tablets**
 - 50mg
 - 100mg
 - 300mg
- **oral syrup**
 - 50mg/5mL
- **injectable solution**
 - 100mg/mL

- **Routes of administration:-**

- Oral route of administration.

➤ **Conclusion: -**

Isoniazid is the most effective drug against Tuberculosis. It is used as a first line antitubercular drug which works by inhibiting mycolic acid synthesis. This paper deals with pharmacokinetic and pharmacodynamic activities of drug. During the study of isoniazid enormous information regarding it has been collected in this review is as clinical trials for isoniazid and detailed information of pharmacovigilance.

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