ISONARIF- rifampin and isoniazid capsule
VersaPharm Incorporated

IsonaRif™ (Rifampin and Isoniazid Capsules USP) 300 mg/150 mg

Rx Only

WARNING

Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment. The risk of developing hepatitis is age related. Approximate case rates by age are: 0 per 1,000 for persons under 20 years of age, 3 per 1,000 for persons in the 20-34 year age group, 12 per 1,000 for persons in the 35-49 year age group, 23 per 1,000 for persons in the 50-64 year age group, and 8 per 1,000 for persons over 65 years of age. The risk of hepatitis is increased with daily consumption of alcohol. Precise data to provide a fatality rate for isoniazid-related hepatitis is not available; however, in a U.S. Public Health Service Surveillance Study of 13,838 persons taking isoniazid, there were 8 deaths among 174 cases of hepatitis.

Therefore, patients given isoniazid should be carefully monitored and interviewed at monthly intervals. Serum transaminase concentration becomes elevated in about 10-20 percent of patients, usually during the first few months of therapy, but it can occur at any time. Usually enzyme levels return to normal despite continuance of drug, but in some cases progressive liver dysfunction occurs. Patients should be instructed to report immediately any of the prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea, or vomiting. If these symptoms appear or if signs suggestive of 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.

Patients with tuberculosis should be given appropriate treatment with alternative drugs. If isoniazid must be reinstituted, it should be reinstituted only after symptoms and laboratory abnormalities have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of recurrent liver involvement. Treatment should be deferred in persons with acute hepatic diseases.

DESCRIPTION

Rifampin/Isoniazid is a combination capsule containing 300 mg rifampin and 150 mg isoniazid. Each capsule for oral administration, contain the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate,magnesium stearate, and pregelatinized starch.

Capsule shell contains: FD&C blue #1, FD&C red #40, gelatin and titanium dioxide.

The printing ink contains: ammonium hydroxide, isopropyl alcohol, N-butyl alcohol, pharmaceutical glaze, propylene glycol, simethicone, and titanium dioxide.

Rifampin is a semisynthetic antibiotic derivative of rifamycin B. The chemical name for rifampin is 3-(4-methyl-1-piperazinyliminomethyl) rifamycin SV.

Isoniazid is the hydrazide of isonicotinic acid. It exists as colorless or white crystals or as a white crystalline powderthat is water soluble, odorless and slowly affected by exposure to air and light.

CLINICAL PHARMACOLOGY

Rifampin

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterialRNA polymerase but does not inhibit the mammalian enzyme. This is the mechanism of action by which rifampinexerts its therapeutic effect. Rifampin cross resistance has only been shown with other rifamycins.

In a study of 14 normal human adult males, peak blood levels of rifampin occurred 1½ to 3 hours following oraladministration of two rifampin and isoniazid capsules. The peaks ranged from 6.9 to 14 mcg/ml with an average of10 mcg/ml.

In normal subjects the T½ (biological half-life) of rifampin in blood is approximately 3 hours. Elimination occursmainly through the bile and, to a much lesser extent, the urine.

Isoniazid

Isoniazid acts against actively growing tubercle bacilli.

After oral administration isoniazid produces peak blood levels within 1 to 2 hours which decline to 50% or lesswithin 6 hours. It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic fluids), tissues, organs,and excreta (saliva, sputum, and feces). The drug also passes through the placental barrier and into milk inconcentrations comparable to those in the plasma. From 50 to 70% of a dose of isoniazid is excreted in the urine in 24 hours.

Isoniazid is metabolized primarily by acetylation and dehydrazination. The rate of acetylation is genetically determined.Approximately 50% of Blacks and Caucasians are "slow inactivators"; the majority of Eskimos and Orientalsare "rapid inactivators."

The rate of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation maylead to higher blood levels of the drug, and thus an increase in toxic reactions.

Pyridoxine deficiency (B6) is sometimes observed in adults with high doses of isoniazid and is considered probablydue to its competition with pyridoxal phosphate for the enzyme apotryptophanase.

INDICATIONS AND USAGE

For pulmonary tuberculosis in which organisms are susceptible, and when the patient has been titrated on theindividual components and it has therefore been established that this fixed dosage is therapeutically effective.

This fixed-dosage combination drug is not recommended for initial therapy of tuberculosis or for preventive therapy.

In the treatment of tuberculosis, small numbers of resistant cells, present within large populations of susceptiblecells, can rapidly become the predominating type. Since rapid emergence of resistance can occur, culture andsusceptibility tests should be performed in the event of persistent positive cultures.

This drug is not indicated for the treatment of meningococcal infections or asymptomatic carriers of *N. meningitides* to eliminate meningococci from the nasopharynx.

CONTRAINDICATIONS

Previous isoniazid-associated hepatic injury; severe adverse reactions to isoniazid, such as drug fever, chills, andarthritis; acute liver disease of any etiology. A history of previous hypersensitivity reaction to any of the rifamycinsor to isoniazid, including drug-induced hepatitis.

WARNINGS

Rifampin and isoniazid capsules are a combination of two drugs, each of which has been associated

with liverdysfunction. Liver function tests should be performed prior to therapy with rifampin/isoniazid and periodicallyduring treatment.

Rifampin

Rifampin has been shown to produce liver dysfunction. There have been fatalities associated with jaundice inpatients with liver disease or receiving rifampin concomitantly with other hepatoxic agents. Since an increased riskmay exist for individuals with liver disease, benefits must be weighed carefully against the risk of further liver damage.

Several studies of tumorigenicity potential have been done in rodents. In one strain of mice known to be particularlysusceptible to the spontaneous development of hepatomas, rifampin given at a level 2-10 times the maximumdosage used clinically resulted in a significant increase in the occurrence of hepatomas in female mice of this strainafter one year of administration.

There was no evidence of tumorigenicity in the males of this strain, in males or females of another mouse strain, orin rats.

Isoniazid

See the boxed warning.

PRECAUTIONS

Rifampin

Rifampin is not recommended for intermittent therapy; the patient should be cautioned against intentional oraccidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reportedwhen therapy was resumed in such cases.

Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. The causeof the phenomenon is unknown. In patients receiving anticoagulants and rifampin concurrently, it is recommendedthat the prothrombin time be performed daily or as frequently as necessary to establish and maintain the requireddose of anticoagulant. Urine, feces, saliva, sputum, sweat, and tears may be colored red-orange by rifampin and itsmetabolites. Soft contact lenses may be permanently stained. Individuals to be treated should be made aware of these possibilities.

It has been reported that the reliability of oral contraceptives may be affected in some patients being treated fortuberculosis with rifampin in combination with at least one other antituberculosis drug. In such cases, alternativecontraceptive measures may need to be considered.

It has also been reported that rifampin given in combination with other antituberculosis drugs may decrease thepharmacologic activity of methadone, oral hypoglycemics, digitoxin, quinidine, disopyramide, dapsone, and corticosteroids.In these cases, dosage adjustment of the interacting drugs is recommended.

Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate andvitamin B12. Alternative methods must be considered when determining folate and vitamin B12 concentrations inthe presence of rifampin.

Since rifampin has been reported to cross the placental barrier and appear in cord blood and in maternal milk,neonates and newborns of rifampin-treated mothers should be carefully observed for any evidence of untowardeffects.

Isoniazid

All drugs should be stopped and an evaluation of the patient should be made at the first sign of a hypersensitivity reaction.

Use of isoniazid should be carefully monitored in the following:

1. Patients who are receiving phenytoin (diphenylhydantoin) concurrently. Isoniazid may decrease the excretion of phenytoin or may enhance its effects. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant dose should be made.
2. Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis.
3. Patients with current chronic liver disease or severe renal dysfunction.

Periodic ophthalmoscopic examination during isoniazid therapy is recommended when visual symptoms occur.

Usage in Pregnancy and Lactation

Rifampin

Although rifampin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampin,alone or in combination with other antituberculosis drugs, on the human fetus is not known. An increase in congenitalmalformations, primarily spina bifida and cleft palate, has been reported in the offspring of rodents given oral dosesof 150 to 250 mg/kg/day of rifampin during pregnancy.

The possible teratogenic potential in women capable of bearing children should be carefully weighed against thebenefits of therapy.

Isoniazid

It has been reported that in both rats and rabbits, isoniazid may exert an embryocidal effect when administeredorally during pregnancy, although no isoniazid-related congenital anomalies have been found in reproductionstudies in mammalian species (mice, rats, and rabbits). Isoniazid should be prescribed during pregnancy onlywhen therapeutically necessary. The benefit of preventive therapy should be weighed against a possible risk to thefetus. Preventive treatment generally should be started after delivery because of the increased risk of tuberculosisfor new mothers.

Since isoniazid is known to cross the placental barrier and to pass into maternal breast milk, neonates and breastfedinfants of isoniazid treated mothers should be carefully observed for any evidence of adverse effects.

Carcinogenesis:

Isoniazid has been reported to induce pulmonary tumors in a number of strains of mice.

ADVERSE REACTIONS

Rifampin

Nervous system reactions: headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion,visual disturbances, muscular weakness, pain in extremities, and generalized numbness.

Gastrointestinal disturbances: in some patients heartburn, epigastric distress, anorexia, nausea, vomiting, gas,cramps, and diarrhea.

Hepatic reactions: transient abnormalities in liver function tests (e.g., elevations in serum bilirubin, BSP, alkalinephosphatase, serum transaminases) have been observed. Rarely, hepatitis or a shock-like syndrome with hepaticinvolvement and abnormal liver function tests.

Renal reactions: elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, renal insufficiency, and acute renal failure have been noted. These are generallyconsidered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment isresumed following intentional or accidental interruption of a daily dosage regimen, and are reversible when rifampinis discontinued and appropriate therapy instituted.

Hematologic reactions: thrombocytopenia, transient leukopenia, hemolytic anemia; eosinophilia, and decreasedhemoglobin have been observed. Thrombocytopenia has occurred when rifampin and ethambutol were administeredconcomitantly according to an intermittent dose schedule twice weekly and in high doses.

Allergic and immunological reactions: occasionally pruritus, urticaria, rash, pemphigoid reaction, eosinophilia,sore mouth, sore tongue, and exudative conjunctivitis. Rarely, hemolysis, hemoglobinuria, hematuria, renal insufficiencyor acute renal failure, have been reported which are generally considered to be hypersensitivity reactions.These have usually occurred during intermittent therapy or when treatment was resumed following intentional oraccidental interruption of a daily dosage regimen and were reversible when rifampin was discontinued and appropriatetherapy instituted.

Although rifampin has been reported to have an immunosuppressive effect in some animal experiments, availablehuman data indicate that this has no clinical significance.

Metabolic reactions: elevations in BUN and serum uric acid have occurred.

Miscellaneous reactions: fever and menstrual disturbances have been noted.

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 mostoften in the malnourished and in those predisposed to neuritis (e.g., alcoholics and diabetics); and is usuallypreceded 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.

Gastrointestinal reactions: nausea, vomiting, and epigastric distress.

Hepatic reactions: elevated serum transaminases (SGOT; SGPT), bilirubinemia, bilirubinuria, jaundice, andoccasionally severe and sometimes fatal hepatitis. The common prodromal symptoms are anorexia, nausea, vomiting, fatigue, malaise, and weakness. Mild and transient elevations of serum transaminase levels occur in 10 to 20percent of persons taking isoniazid. The abnormality usually occurs in the first 4 to 6 months of treatment but canoccur at any time during therapy. In most instances, enzyme levels return to normal with no necessity to discontinuemedication. In occasional instances, progressive liver damage occurs, with accompanying symptoms. In thesecases, the drug should be discontinued immediately. The frequency of progressive liver damage increases withage. It is rare in persons under 20, but occurs in up to 2.3 percent of those over 50 years of age.

Hematologic reactions: agranulocytosis, hemolytic sideroblastic or aplastic anemia, thrombocytopenia, andeosinophilia.

Hypersensitivity reactions: fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy,and vasculitis.

Metabolic and endocrine reactions: pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, andgynecomastia.

Miscellaneous reactions: rheumatic syndrome and systemic lupus erythematosus-like syndrome.

OVERDOSAGE

Rifampin

Signs and Symptoms: Nausea, vomiting and increasing lethargy will probably occur within a short time after ingestion;actual unconsciousness may occur with severe hepatic involvement. Brownish-red or orange discoloration ofthe skin, urine, sweat, saliva, tears, and feces is proportional to amount

ingested.

Liver enlargement, possibly with tenderness, can develop within a few hours after severe overdosage, and jaundicemay develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function.Other physical findings remain essentially normal.

Direct and total bilirubin levels may increase rapidly with severe overdosage; hepatic enzyme levels may be affected, especially with prior impairment of hepatic function. A direct effect upon hemopoietic system, electrolyte levels, or acid-base balance is unlikely.

Isoniazid

Signs and Symptoms: Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurring of speech, blurring of vision, visual hallucinations (including bright colors and strangedesigns), are among the early manifestations. With marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, are to be expected, along with severe, intractable seizures.Severe metabolic acidosis, acetonuria, and hyperglycemia are typical laboratory findings.

Treatment

The airway should be secured and adequate respiratory exchange established. Only then should gastric emptying(lavage-aspiration) be attempted; this may be difficult because of seizures. Since nausea and vomiting are likely tobe present, gastric lavage is probably preferable to induction of emesis.

Activated charcoal slurry instilled into the stomach following evacuation of gastric contents can help absorb anyremaining drug in the GI tract. Antiemetic medication may be required to control severe nausea and vomiting.

Blood samples should be obtained for immediate determination of gases, electrolytes, BUN, glucose, etc. Bloodshould be typed and cross matched in preparation for possible hemodialysis.

Rapid control of metabolic acidosis is fundamental to management. Intravenous sodium bicarbonate should begiven at once and repeated as needed, adjusting subsequent dosage on the basis of laboratory findings (i.e., serumsodium, pH, etc.). At the same time, anticonvulsants should be given intravenously (i.e., barbiturates, diphenylhydantoin, diazepam) as required, and large doses of intravenous pyridoxine.

Forced osmotic diuresis must be started early and should be continued for some hours after clinical improvementto hasten renal clearance of drug and help prevent relapse. Fluid intake and output should be monitored.

Bile drainage may be indicated in presence of serious impairment of hepatic function lasting more than 24-48hours. Under these circumstances and for severe cases, extracorporeal hemodialysis may be required; if this is notavailable, peritoneal dialysis can be used along with forced diuresis.

Along with measures based on initial and repeated determination of blood gases and other laboratory tests as needed,meticulous respiratory and other intensive care should be utilized to protect against hypoxia, hypotension, aspiration,pneumonitis, etc.

In patients with previously adequate hepatic function, reversal of liver enlargement and impaired hepatic excretoryfunction probably will be noted within 72 hours, with rapid return toward normal thereafter.

Untreated or inadequately treated cases of gross isoniazid overdosage can terminate fatally, but good response hasbeen reported in most patients brought under adequate treatment within the first few hours after drug ingestion.

DOSAGE AND ADMINISTRATION

In general, therapy should be continued until bacterial conversion and maximal improvement have occurred.

Adults: Two Rifampin and Isoniazid Capsules, USP (600 mg rifampin, 300 mg isoniazid) once daily, administeredone hour before or two hours after a meal.

Concomitant administration of pyridoxine (B6) is recommended in the malnourished, in those predisposed toneuropathy (e.g., diabetic), and in adolescents.

Susceptibility Testing, Rifampin

Rifampin susceptibility powders are available for both direct and indirect methods of determining the susceptibility of strains of mycobacteria. The MIC's of susceptible clinical isolates when determined in 7H10 or other non-eggcontainingmedia have ranged from 0.1 to 2 mcg/mL. Quantitative methods that require measurement of zonediameters give the most precise estimates of antibiotic susceptibility. One such procedure has been recommendedfor use with discs for testing susceptibility to rifampin. Interpretations correlate zone diameters from the disc testwith MIC (minimal inhibitory concentration) values for rifampin.

HOW SUPPLIED

Rifampin and Isoniazid Capsules USP, 300 mg/150 mg are supplied as red powder filled No. 0 Scarlet Opaque HardGelatin Capsules; printed "IsonaRif™" on one end and “VP/017” on the other end in white ink; bottles of 60 capsules (NDC#61748-017-60).

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep tightly closed. Store in a dry place. Avoid excessive heat.

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured for:

VersaPharm Incorporated

Marietta, GA 30062

Manufactured by:

West-ward Pharmaceutical Corp

Eatontown, NJ 07724

Rev. Feb. 2007

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

NDC 61748-017-60

IsonaRif™

300/150 mg

R_x Only

60 Capsules

ISONARIF

rifampin and isoniazid capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61748-017
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
RIFAMPIN (UNII: VJT6J7R4TR) (RIFAMPIN - UNII:VJT6J7R4TR)	RIFAMPIN	300 mg
ISONIAZID (UNII: V83O1VOZ8L) (ISONIAZID - UNII:V83O1VOZ8L)	ISONIAZID	150 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
AMMONIA (UNII: 5138Q19F1X)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
DIMETHICONE (UNII: 92RU3N3Y1O)	

Product Characteristics			
Color	RED (OPAQUE)	**Score**	no score

Shape	CAPSULE (CAPSULE)	**Size**	20mm
Flavor		**Imprint Code**	IsonaRif;VP;017
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61748-017-60	60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065221	09/01/2005	

Labeler - VersaPharm Incorporated (956741896)

Revised: 3/2012 VersaPharm Incorporated