Lederrif®
(Rifampicin)

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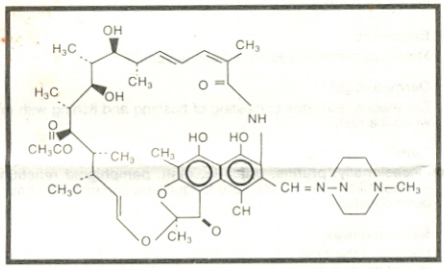
DESCRIPTION

Lederrif® Rifampicin results from a condensation reaction between 3-formylrifamycin SV and 1-amino 4-methylpiperazine.



ACTIONS

Lederrif® inhibits RNA-polymerase activity in susceptible bacterial cells, but it does not inhibit the mammalian enzyme at comparable concentrations. This is the mechanism by which rifampicin exerts its bactericidal activity against most groups of Mycobacteria. Cross resistance to rifampicin has been shown only with other rifamycins.

HUMAN PHARMACOLOGY

Lederrif® is readily absorbed from the gastrointestinal tract. Peak blood levels in normal adults vary widely among individuals. Peak levels occur in 2 to 4 hours following the oral administration of a 600 mg dose. The average peak value is 7 mcg/ml with a range of 4-32 mcg/ml.

The serum half-life of **Lederrif**® in adults and children is approximately 3 hours and is increased in the presence of hepatic dysfunction. It remains unchanged in those with renal insufficiency or in those undergoing hemodialysis or peritoneal dialysis. Following absorption from the gastrointestinal tract, **Lederrif**® is rapidly eliminated in the bile and an enterohepatic circulation ensues. During this process the drug is progressively deacetylated so that nearly all the drug is in this form in about 6 hours. This metabolite is microbiologically active.

Upto 30% of a dose is excreted in the urine, with about half of this being unchanged drug. **Lederrif**® is about 80% protein bound. **Lederrif**® crosses the blood-brain barrier, the placental barrier and is excreted in breast milk.

THERAPEUTIC INDICATIONS

Lederrif® is a major drug in the management of tuberculosis and certain opportunistic mycobacterial infections. It is effective in cases resistant to other antituberculosis agents and shows no cross-resistance outside the rifamycin group of drugs. It is effective in combination with ethambutol, isoniazid, streptomycin, and the majority of second-line drugs. While not generally recommended for combination therapy with PAS, if for any reason this regimen is used, the drugs should be given not less than eight hours apart to assure satisfactory blood levels.

Pulmonary Tuberculosis

In the initial treatment and in retreatment of patients with pulmonary tuberculosis, **Lederrif**® must be used in conjunction with at least one other antituberculosis drug. Frequently used regimens have been the following:

- Isoniazid and rifampicin
- Ethambutol and rifampicin
- Isoniazid, ethambutol and rifampicin

Meningococcal Carriers

Lederrif® is indicated for the treatment of asymptomatic carriers of N.meningitidis to eliminate meningococci from the nasopharynx. The possibility of rapid emergence of resistant meningococci restricts the use of **Lederrif**® to short-term treatment of the asymptomatic carrier state. **Lederrif**® *is not to be used for the treatment of meningococcal infection.*

To avoid the indiscriminate use of **Lederrif**®, diagnostic laboratory procedures including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. In order to preserve the usefulness of **Lederrif**® in the treatment of asymptomatic meningococcal carriers, it is recommended that the drug be reserved for situations in which the risk of meningococcal disease is high.

Both in the treatment of tuberculosis and in the treatment of meningococcal carriers, small numbers of resistant cells, present within large populations of susceptible cells can rapidly become the predominating type. Since rapid emergence of resistance can occur, culture and susceptibility tests should be performed in the event of persistent positive cultures.

POSOLOGY AND METHOD OF ADMINISTRATION

Tuberculosis

Adults and Children: The daily dose range for **Lederrif**® is 10 to 20 mg/kg/day up to 600 mg/day. **Lederrif**® should be administered one hour before or two hours after meals.

In the treatment of tuberculosis **Lederrif**® should always be administered with at least one other antituberculosis drug. In general, therapy for tuberculosis should be continued for 6 to 9 months or until at least 6 months have elapsed from conversion of sputum to culture negativity.

There is no data available on the safety of **Lederrif**® in children less than 5 years of age.

Resumption of Therapy

When resuming treatment with **Lederrif**® after a prolonged interval, the drug should be given in small, gradually increasing doses in adults, initially, 150 mg/day, increasing gradually by 150 mg/day until the desired daily dose is reached. During this period, renal function should be monitored closely. Therapy should be discontinued permanently if renal failure, thrombocytopenia, purpura or hemolytic anemia appear.

Meningococcal carriers

Adults:

For adults, it is recommended that 600 mg **Lederrif**® be administered twice daily for two days.

Infants and Children: 1 month of age or older:
10 mg/kg every 12 hours for two days.

Children under 1 month of age:
5 mg/kg every 12 hours for two days.

Susceptibility testing:

Pulmonary tuberculosis:

Lederrif® susceptibility powders are available for both direct and indirect methods of determining the susceptibility of strains of mycobacteria. The MICs (minimal inhibitory concentration) of susceptible clinical isolates when determined in 7H10 or other non-egg-containing media have ranged from 0.1 to 2 mcg/ml.

Meningococcal carriers:

Susceptibility discs containing 5 mcg of **Lederrif**® are available for susceptibility testing of N. meningitidis.

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs for testing susceptibility to **Lederrif**®. interpretations correlate zone diameters from the discs test with MIC values for **Lederrif**®. A range of MICs from 0.1 to 1 mcg/ml has been found in vitro for susceptible strains of N.*meningitidis*. With this procedure, a report from the laboratory of "resistant" indicates that the organism is not likely to be eradicated from the nasopharynx of asymptomatic carriers.

CONTRAINDICATIONS

Lederrif® is contraindicated during pregnancy because teratogenic effects have been demonstrated in animals on very high doses. It is also contraindicated in patients with jaundice and in those with known hypersensitivity to rifamycins.

Precautions

Lederrif® is not recommended for intermittent therapy. The patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases.

Lederrif® is a potent inducer of liver enzymes. Thus, the metabolism of certain concomitantly administered drugs may be increased, including oral anticoagulants, corticosteroids, oral contraceptives, oral antidiabetic agents, cyclosporine, quinidine, digitalis derivatives, diazepam, verapamil, beta-adrenergic blockers, clofibrate, disopyramide, mexiletine, theophylline, chloramphenicol, anticonvulsants, dapsone and methadone, larger doses being needed when **Lederrif**® therapy is initiated and a reduction when withdrawn.

In patients receiving anticoagulants and **Lederrif**® concurrently, it is recommended that daily prothrombin times be done or as frequently as necessary to establish and maintain the required dose of anticoagulant. Rifampicin has been observed to increase the requirement for anticoagulant drugs of the coumarin type.

It has been reported that the reliability of oral contraceptives may be affected in patients being treated for tuberculosis with rifampicin in combination with at least one other antituberculosis drug. In such cases, alternative contraceptive measures may need to be considered.

When **Lederrif®** is taken with paraaminosalicyclic acid (PAS), rifampicin levels in the serum may decrease. Therefore, the drugs should be taken 8 hours apart. Probenecid has been reported to increase **Lederrif®** blood levels.

Halothane, when given concomitantly with **Lederrif®** has been reported to increase the hepatotoxicity of both drugs. Ketoconazole, when given concomitantly with **Lederrif®** has been reported to diminish the serum concentration of both drugs. Dosage should be adjusted if indicated by the patient's clinical condition.

Transient abnormalities in liver function tests (e.g. elevation in serum bilirubin, abnormal bromsulphalein (BSP) excretion, alkaline phosphatase, and serum transaminases) and reduced biliary excretion of contrast media used for visualization of the gall bladder have also been observed. Therefore, these tests should be performed before the morning dose of **Lederrif®**.

Because of the potential toxicity, **Lederrif®** should be used with extreme caution in elderly patients.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Urine, faeces, saliva, sputum, sweat and tears may be colored red-orange by **Lederrif®** and its metabolites. Soft contact lenses may be permanently stained. Individuals to be treated should be made aware of these possibilities.

Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and vitamin B12. Thus alternate assay methods should be considered.

Neonates of Lederrif® treated mothers

Since **Lederrif®** has been reported to cross the placental barrier and appear in cord blood, neonates of **Lederrif®** treated mothers should be carefully observed for any evidence of adverse effects.

WARNINGS

Lederrif® has been shown to produce liver dysfunction. There have been fatalities associated with jaundice in patients with liver disease or receiving **Lederrif®** concomitantly with other hepatotoxic agents. Since an increased risk may exist for individuals with liver disease, benefits must be weighed carefully against the risk of further liver damage. Periodic liver function monitoring is mandatory, especially serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) levels should be monitored prior to therapy and then every two to four weeks during therapy.

If signs of hepatocellular damage occur, **Lederrif®** should be withdrawn. In some cases, hyperbilirubinemia resulting from competition between **Lederrif®** and bilirubin for excretory pathways of the liver at the cell level can occur in the early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition. **Lederrif®** has enzyme-inducing properties, including induction of delta amino levulinic acid synthetase. Isolated reports have associated porphyria exacerbation with **Lederrif®** administration. The possibility of rapid emergence of resistant meningococci restricts the use of **Lederrif®** to short-term treatment of the asymptomatic carrier state. **Lederrif®** *is not to be used for the treatment of meningococcal infection.*

PREGNANCY AND LACTATION

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

The possible teratogenic potential in women capable of bearing children should be weighed carefully against the benefits of therapy. **Lederrif®** is excreted in breast milk. A decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

Gastrointestinal

Heartburn, epigastric distress, anorexia, nausea, vomiting, jaundice, flatulence, cramps and diarrhea have been noted in some patients. Although C. difficile has been shown in vitro to be sensitive to rifampicin, pseudomembranous colitis has been reported with the use of rifampicin. Therefore it is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Rarely hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests has been reported. Transient abnormalities in liver function tests (e.g. elevations in serum bilirubin, BSP, alkaline phosphatase, serum transminases) have been observed.

Central Nervous System

Headache, drowsiness, fatigue, dizziness, inability to concentrate, mental confusion, visual disturbances, muscular weakness, fever, pains in extremities and generalized numbness have been observed. Rare reports of myopathy have also been reported.

Hematologic

Thrombocytopenia, transient leukopenia, hemolytic anemia and decreased hemoglobin have been observed. Thrombocytopenia is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when **Lederrif®** administration has been continued or resumed after the appearance of purpura.

Renal

Elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, renal insufficiency, and acute renal failure have been reported. These are generally considered to be hypersensitivity reactions and are reversible when **Lederrif®** is discontinued and appropriate therapy instituted.

Endocrine

Menstrual disturbances have been observed.

Dermatologic

Cutaneous reactions consisting of flushing and itching with or without a rash.

Hypersensitivity Reactions

Occasionally, pruritis, urticaria, rash, pemphigoid reaction eosinophilia, sore mouth, sore tongue and conjunctivitis have been observed.

Miscellaneous

Edema of the face and extremities has been reported. Other reactions reported to have occurred with intermittent dosage regimens include "flu" syndrome (such as episodes of fever, chills, headache, dizziness, and bone pain) shortness of breath, wheezing, decrease in blood pressure, and shock. The "flu" syndrome may also appear if rifampicin is taken irregularly by the patients or if daily administration is resumed after a drug free interval.

OVERDOSAGE

Signs and Symptoms:

Nausea, vomiting, and increasing lethargy will probably occur within a short time after ingestion; unconsciousness may occur when there is severe hepatic disease. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears and faeces is proportional to the amount ingested.

Liver enlargement, possibly with tenderness, may develop within a few hours after severe overdosage and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal. 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 the hematopoietic system, electrolyte levels, or acid-base balance is unlikely.

TREATMENT

Gastric lavage fallowed by activated charcoal slurry instilled into the stomach following evacuation of gastric contents could help to absorb any remaining drug in the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting. Active diuresis (with measured intake and output) will help to promote excretion of the drug. Bile drainage may be indicated in the presence of serious impairment of hepatic function lasting more than 24 - 48 hours; under these circumstances, extracorporeal hemodialysis may be required. In patients with previously adequate hepatic function, reversal of liver enlargement and impaired hepatic excretory function probably will be noted within 72 hours with rapid return toward normal thereafter.

SHELF LIFE

24 months.

SPECIAL PRECAUTIONS FOR STORAGE

Protect from heat and moisture. (Tablet)

Protect from heat and light. (Suspension)

Keep all medicines out of the reach of children.

HOW SUPPLIED

Blister of film Coated tablets

PC 5243 300 mg tablets 3x10's

PC 5244 450 mg tablets 3x10's

PC 5232 600 mg tablets 3x10's

Suspension

PC 8498 20mg/ml 60 ml glass Bottles

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Manufactured by :
Wyeth Pakistan Limited,
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Wyeth®