

Bone Marrow Suppression: RETROVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count $<1,000$ cells/mm³ or hemoglobin <9.5 g/dL. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed. There have been reports of pancytopenia associated with the use of RETROVIR, which was reversible in most instances after discontinuance of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of RETROVIR, and/or blood transfusions, has occurred during treatment with RETROVIR alone or in combination with other antiretrovirals.

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with RETROVIR. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

Myopathy: Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of RETROVIR.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zidovudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering RETROVIR to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with RETROVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

General: Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function ($\text{CrCl} < 15$ mL/min), dosage reduction is recommended. Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function which may increase the risk of hematologic toxicity (see CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Fat Redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance,” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients: RETROVIR is not a cure for HIV infection, and patients may continue to acquire illnesses associated with HIV infection, including opportunistic infections.

Therefore, patients should be advised to seek medical care for any significant change in their health status.

The safety and efficacy of RETROVIR in women, intravenous drug users, and racial minorities is not significantly different than that observed in white males.

Patients should be informed that the major toxicities of RETROVIR are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or drug discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon-alpha, that may exacerbate the toxicity of RETROVIR (see PRECAUTIONS: Drug Interactions). Patients should be informed that other adverse effects of RETROVIR include nausea and vomiting. Patients should also be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with RETROVIR.

RETROVIR Tablets, Capsules, and Syrup are for oral ingestion only. Patients should be told of the importance of taking RETROVIR exactly as prescribed. They should be told not to share medication and not to exceed the recommended dose. Patients should be told that the long-term effects of RETROVIR are unknown at this time.

Pregnant women considering the use of RETROVIR during pregnancy for prevention of HIV-transmission to their infants should be advised that transmission may still occur in some cases despite therapy. The long-term consequences of in utero and infant exposure to RETROVIR are unknown, including the possible risk of cancer.

HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Patients should be advised that therapy with RETROVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions: See CLINICAL PHARMACOLOGY section (Table 4) for information on zidovudine concentrations when coadministered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

Antiretroviral Agents: Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated in vitro.

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of RETROVIR against HIV; concomitant use of such drugs should be avoided.

Doxorubicin: Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic relationship has been demonstrated in vitro (see CLINICAL PHARMACOLOGY for additional drug interactions).

Phenytoin: Phenytoin plasma levels have been reported to be low in some patients receiving RETROVIR, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

Overlapping Toxicities: Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or

~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Zidovudine was mutagenic in a 5178Y/TK[±] mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Pregnancy: Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated area-under-the-curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given 600 mg per day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Two rodent transplacental carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, Impairment of Fertility).

A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of RETROVIR for the prevention of maternal-fetal HIV-transmission (see INDICATIONS AND USAGE: Description of Clinical Studies). Congenital abnormalities occurred with similar frequency between neonates born to mothers who received RETROVIR and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to RETROVIR, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission

of HIV. Zidovudine is excreted in human milk (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers). Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving RETROVIR** (see Pediatric Use and INDICATIONS AND USAGE: Maternal-Fetal HIV Transmission).

Pediatric Use: RETROVIR has been studied in HIV-infected pediatric patients over 3 months of age who had HIV-related symptoms or who were asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression. RETROVIR has also been studied in neonates perinatally exposed to HIV (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, INDICATIONS AND USAGE: Description of Clinical Studies, and CLINICAL PHARMACOLOGY: Pharmacokinetics).

Geriatric Use: Clinical studies of RETROVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adults: The frequency and severity of adverse events associated with the use of RETROVIR are greater in patients with more advanced infection at the time of initiation of therapy.

Table 6 summarizes events reported at a statistically significant greater incidence for patients receiving RETROVIR in a monotherapy study:

Table 6. Percentage (%) of Patients with Adverse Events* in Asymptomatic HIV Infection (ACTG019)

| Adverse Event | RETROVIR 500 mg/day (n = 453) | Placebo (n = 428) |
|-------------------------|----------------------------------|----------------------|
| Body as a whole | | |
| Asthenia | 8.6% [†] | 5.8% |
| Headache | 62.5% | 52.6% |
| Malaise | 53.2% | 44.9% |
| Gastrointestinal | | |
| Anorexia | 20.1% | 10.5% |
| Constipation | 6.4% [†] | 3.5% |
| Nausea | 51.4% | 29.9% |
| Vomiting | 17.2% | 9.8% |

*Reported in $\geq 5\%$ of study population.

[†]Not statistically significant versus placebo.

In addition to the adverse events listed in Table 6, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

Selected laboratory abnormalities observed during a clinical study of monotherapy with RETROVIR are shown in Table 7.

Table 7. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients with Asymptomatic HIV Infection (ACTG019)

| Adverse Event | RETROVIR 500 mg/day (n = 453) | Placebo (n = 428) |
|--|----------------------------------|----------------------|
| Anemia (Hgb < 8 g/dL) | 1.1% | 0.2% |
| Granulocytopenia (< 750 cells/mm ³) | 1.8% | 1.6% |
| Thrombocytopenia (platelets < 50,000/mm ³) | 0% | 0.5% |
| ALT (> 5 x ULN) | 3.1% | 2.6% |
| AST (> 5 x ULN) | 0.9% | 1.6% |
| Alkaline phosphatase (> 5 x ULN) | 0% | 0% |

ULN = Upper limit of normal.

Pediatrics: Study ACTG300: Selected clinical adverse events and physical findings with a $\geq 5\%$ frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m² 3 times daily compared with didanosine in therapy-naïve (≤ 56 days of antiretroviral therapy) pediatric patients are listed in Table 8.

Table 8. Selected Clinical Adverse Events and Physical Findings ($\geq 5\%$ Frequency) in Pediatric Patients in Study ACTG300

| Adverse Event | EPIVIR plus RETROVIR (n = 236) | Didanosine (n = 235) |
|---------------------------------|--------------------------------------|-------------------------|
| Body as a whole | | |
| Fever | 25% | 32% |
| Digestive | | |
| Hepatomegaly | 11% | 11% |
| Nausea & vomiting | 8% | 7% |
| Diarrhea | 8% | 6% |
| Stomatitis | 6% | 12% |
| Splenomegaly | 5% | 8% |
| Respiratory | | |
| Cough | 15% | 18% |
| Abnormal breath sounds/wheezing | 7% | 9% |
| Ear, Nose, and Throat | | |
| Signs or symptoms of ears* | 7% | 6% |
| Nasal discharge or congestion | 8% | 11% |
| Other | | |
| Skin rashes | 12% | 14% |
| Lymphadenopathy | 9% | 11% |

*Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤ 56 days of antiretroviral therapy) pediatric patients are listed in Table 9.

Table 9. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG300

| Test (Abnormal Level) | EPIVIR plus RETROVIR | Didanosine |
|--|-------------------------|------------|
| Neutropenia (ANC<400 cells/mm ³) | 8% | 3% |
| Anemia (Hgb<7.0 g/dL) | 4% | 2% |
| Thrombocytopenia (platelets<50,000/mm ³) | 1% | 3% |
| ALT (>10 x ULN) | 1% | 3% |
| AST (>10 x ULN) | 2% | 4% |
| Lipase (>2.5 x ULN) | 3% | 3% |
| Total amylase (>2.5 x ULN) | 3% | 3% |

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

Additional adverse events reported in open-label studies in pediatric patients receiving RETROVIR 180 mg/m² every 6 hours were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/irritability, and weight loss.

The clinical adverse events reported among adult recipients of RETROVIR may also occur in pediatric patients.

Use for the Prevention of Maternal-Fetal Transmission of HIV: In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of RETROVIR for the prevention of maternal-fetal HIV transmission, RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm³). Anemia occurred in 22% of the neonates who received RETROVIR and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving RETROVIR compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with RETROVIR. Neutropenia was reported with similar frequency in the group that received RETROVIR (21%) and in the group that received placebo (27%). The long-term consequences of in utero and infant exposure to RETROVIR are unknown.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during use of RETROVIR in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to RETROVIR, or a combination of these factors.

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Cardiovascular: Cardiomyopathy, syncope.

Endocrine: Gynecomastia.

Eye: Macular edema.

Gastrointestinal: Constipation, dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.

Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.

Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.

Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

Respiratory: Cough, dyspnea, rhinitis, sinusitis.

Skin: Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.

Urogenital: Urinary frequency, urinary hesitancy.

OVERDOSAGE

Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. No specific symptoms or signs have been identified following acute overdosage with zidovudine apart from those listed as adverse events such as fatigue, headache, vomiting, and occasional reports of hematological disturbances. All patients recovered without permanent sequelae. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine while elimination of its primary metabolite, GZDV, is enhanced.

DOSAGE AND ADMINISTRATION

Adults: The recommended oral dose of RETROVIR is 600 mg per day in divided doses in combination with other antiretroviral agents.

Pediatrics: The recommended dose in pediatric patients 6 weeks to 12 years of age is 160 mg/m² every 8 hours (480 mg/m²/day up to a maximum of 200 mg every 8 hours) in combination with other antiretroviral agents.

Maternal-Fetal HIV Transmission: The recommended dosing regimen for administration to pregnant women (>14 weeks of pregnancy) and their neonates is:

Maternal Dosing: 100 mg orally 5 times per day until the start of labor (see INDICATIONS AND USAGE: Description of Clinical Studies). During labor and delivery, intravenous

RETROVIR should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous intravenous infusion of 1 mg/kg/hour (total body weight) until clamping of the umbilical cord.

Neonatal Dosing: 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered RETROVIR intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See PRECAUTIONS if hepatic disease or renal insufficiency is present.)

Monitoring of Patients: Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia (see WARNINGS). In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

Dose Adjustment: Anemia: Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm³ or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (see WARNINGS). In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance.

For patients experiencing pronounced anemia while receiving chronic coadministration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

End-Stage Renal Disease: In patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6 to 8 hours (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Hepatic Impairment: There are insufficient data to recommend dose adjustment of RETROVIR in patients with mild to moderate impaired hepatic function or liver cirrhosis. Since RETROVIR is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be necessary in these patients. Frequent monitoring for hematologic toxicities is advised (see CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: General).

HOW SUPPLIED

RETROVIR Tablets 300 mg (biconvex, white, round, film-coated) containing 300 mg zidovudine, one side engraved "GX CW3" and "300" on the other side. Bottle of 60 (NDC 0173-0501-00).

Store at 15° to 25°C (59° to 77°F).

RETROVIR Capsules 100 mg (white, opaque cap and body with a dark blue band) containing 100 mg zidovudine and printed with “Wellcome” and unicorn logo on cap and “Y9C” and “100” on body. Bottles of 100 (NDC 0173-0108-55) and Unit Dose Pack of 100 (NDC 0173-0108-56).

Store at 15° to 25°C (59° to 77°F) and protect from moisture.

RETROVIR Syrup (colorless to pale yellow, strawberry-flavored) containing 50 mg zidovudine in each teaspoonful (5 mL). Bottle of 240 mL (NDC 0173-0113-18) with child-resistant cap.

Store at 15° to 25°C (59° to 77°F).



GlaxoSmithKline
Research Triangle Park, NC 27709

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RL-1194

SULFADIAZINE - sulfadiazine tablet

Eon Labs, Inc.

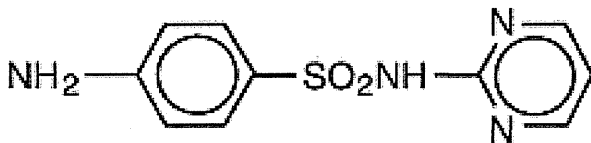
Rx only

DESCRIPTION

Sulfadiazine is an oral sulfonamide anti-bacterial agent.

Each tablet, for oral administration, contains 500 mg sulfadiazine. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, docusate sodium, microcrystalline cellulose, povidone, sodium benzoate, sodium starch glycolate and stearic acid.

Sulfadiazine occurs as a white or slightly yellow powder. It is odorless or nearly so and slowly darkens on exposure to light. It is practically insoluble in water and slightly soluble in alcohol. The chemical name of sulfadiazine is N¹-2-pyrimidinylsulfanilamide. The molecular formula is C₁₀H₁₀N₄O₂S. It has a molecular weight of 250.27. The structural formula is shown below:



Most sulfonamides slowly darken on exposure to light.

CLINICAL PHARMACOLOGY

The systemic sulfonamides are bacteriostatic agents having a similar spectrum of activity. Sulfonamides competitively inhibit bacterial synthesis of folic acid (pteroylglutamic acid) from aminobenzoic acid. Resistant strains are capable of utilizing folic acid precursors or preformed folic acid.

Sulfonamides exist in the blood in 3 forms - free, conjugated (acetylated and possibly others) and protein bound. The free form is considered to be the therapeutically active one.

Sulfadiazine given orally is readily absorbed from the gastrointestinal tract. After a single 2 g oral dose, a peak of 6.04 mg/100 mL is reached in 4 hours; of this, 4.65 mg/100 mL is free drug.

When a dose of 100 mg/kg of body weight is given initially and followed by 50 mg/kg every 6 hours, blood levels of free sulfadiazine are about 7 mg/100mL. Protein binding is 38% to 48%. Sulfadiazine diffuses into the cerebrospinal fluid; free drug reaches 32% to 65% of blood levels and total drug 40% to 60%.

Sulfadiazine is excreted largely in the urine, where concentrations are 10 to 25 times greater than serum levels. Approximately 10% of a single oral dose is excreted in the first 6 hours, 50% within 24 hours and 60% to 85% in 48 to 72 hours. Of the amount excreted in the urine, 15% to 40% is in the acetyl form.

INDICATIONS AND USAGE

Sulfadiazine tablets are indicated in the following conditions:

Chancroid

Trachoma

Inclusion conjunctivitis

Nocardiosis

Urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) in the absence of obstructive uropathy or foreign bodies, when these infections are caused by susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Staphylococcus aureus*, *Proteus mirabilis* and *P. vulgaris*. Sulfadiazine should be used for urinary tract infections only after use of more soluble sulfonamides has been unsuccessful.

Toxoplasmosis encephalitis in patients with and without acquired immunodeficiency syndrome, as adjunctive therapy with pyrimethamine.

Malaria due to chloroquine-resistant strains of *Plasmodium falciparum*, when used as adjunctive therapy.

Prophylaxis of meningococcal meningitis when sulfonamide-sensitive group A strains are known to prevail in family groups or larger closed populations (the prophylactic usefulness of sulfonamides when group B or C infections are prevalent is not proved and may be harmful in closed population groups).

Meningococcal meningitis, when the organism has been demonstrated to be susceptible.

Acute otitis media due to *Haemophilus influenzae*, when used concomitantly with adequate doses of penicillin.

Prophylaxis against recurrences of rheumatic fever, as an alternative to penicillin.

H. influenzae meningitis, as adjunctive therapy with parental streptomycin.

IMPORTANT NOTES

In vitro sulfonamide susceptibility tests are not always reliable. The test must be carefully coordinated with bacteriologic and clinical response. When the patient is already taking sulfonamides, follow-up cultures should have aminobenzoic acid added to the culture media.

Currently, the increasing frequency of resistant organisms limits the usefulness of antibacterial agents, including the sulfonamides, especially in the treatment of recurrent and complicated urinary tract infections.

Wide variation in blood levels may result with identical doses. Blood levels should be measured in patients receiving sulfonamides for serious infections. Free sulfonamide blood levels of 5 to 15 mg per 100 mL may be considered therapeutically effective for most infections and blood levels of 12 to 15 mg per 100 mL may be considered optimal for serious infections. Twenty mg per 100 mL should be the maximum total sulfonamide level, since adverse reactions occur more frequently above this level.

CONTRAINDICATIONS

Sulfadiazine is contraindicated in the following circumstances: Hypersensitivity to sulfonamides.

In infants less than 2 months of age (except as adjunctive therapy with pyrimethamine in the treatment of congenital toxoplasmosis). In pregnancy at term and during the nursing period, because sulfonamides cross the placenta and are excreted in breast milk and may cause kernicterus.

WARNINGS

The sulfonamides should not be used for the treatment of group A beta-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever and glomerulonephritis. Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias.

The presence of such clinical signs as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders.

The frequency of renal complications is considerably lower in patients receiving the more soluble sulfonamides.

PRECAUTIONS

General

Sulfonamides should be given with caution to patients with impaired renal or hepatic function and to those with severe allergy or bronchial asthma.

Hemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase. This reaction is dose related.

Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

Information for Patients

Patients should be instructed to drink an eight ounce glass of water with each dose of medication and at frequent intervals throughout the day. Caution patients to report promptly the onset of sore throat, fever, pallor, purpura or jaundice when taking this drug, since these may be early indications of serious blood disorders.

Laboratory Tests

Complete blood counts and urinalyses with careful microscopic examinations should be done frequently in patients receiving sulfonamides.

Drug Interactions

Administration of a sulfonamide may increase the effect of oral anticoagulants and methotrexate, probably by displacement of these drugs from binding sites on plasma albumin. Potentiation of the action of sulfonamide hypoglycemic agents, thiazide diuretics and uricosuric agents may also be noted. This may also be due to displacement of the drugs from albumin or a pharmacodynamic mechanism may play a role. Conversely, agents such as indomethacin, probenecid and salicylates may displace sulfonamides from plasma albumin and increase the concentrations of free drug in plasma.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The sulfonamides bear certain chemical similarities to some goitrogens. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides and long-term administration has produced thyroid malignancies in rats.

Pregnancy

Teratogenic Effects

Pregnancy Category C

The safe use of sulfonamides in pregnancy has not been established. The teratogenic potential of most sulfonamides has not been thoroughly investigated in either animals or humans. However, a significant increase in the incidence of cleft palate and other bony abnormalities in offspring has been observed when certain sulfonamides of the short, intermediate and long acting types were given to pregnant rats and mice in high oral doses (7 to 25 times the human therapeutic dose).

Nursing Mothers

Sulfadiazine is contraindicated for use in nursing mothers because the sulfonamides cross the placenta, are excreted in breast milk and may cause kernicterus.

Because of the potential for serious adverse reactions in nursing infants from sulfadiazine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. See **CONTRAINDICATIONS**.

Pediatric Use

Sulfadiazine is contraindicated in infants less than 2 months of age (except as adjunctive therapy with pyrimethamine in the treatment of congenital toxoplasmosis). See **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**.

ADVERSE REACTIONS

Blood Dyscrasias

Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, and methemoglobinemia.

Allergic Reactions

Erythema multiforme (Stevens-Johnson syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, allergic myocarditis, drug fever, and chills.

Gastrointestinal Reactions

Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis, and stomatitis.

C.N.S. Reactions

Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, and insomnia.

Renal

Crystalluria, stone formation, toxic nephrosis with oliguria and anuria; periarteritis nodosa and lupus erythematosus phenomenon have been noted.

Miscellaneous Reactions

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents.

DOSAGE AND ADMINISTRATION

SYSTEMIC SULFONAMIDES ARE CONTRAINDICATED IN INFANTS UNDER 2 MONTHS OF AGE except as adjunctive therapy with pyrimethamine in the treatment of congenital toxoplasmosis.

Usual Dosage for Infants over 2 Months of Age and Children

Initially, one-half the 24-hour dose. Maintenance, 150 mg/kg or 4 g/m², divided into 4 to 6 doses, every 24 hours, with a maximum of 6 g every 24 hours. Rheumatic fever prophylaxis, under 30 kg (66 pounds), 500 mg every 24 hours; over 30 kg (66 pounds), 1 g every 24 hours.

Usual Adult Dosage

Initially, 2 to 4 g. Maintenance, 2 to 4 g, divided into 3 to 6 doses, every 24 hours.

HOW SUPPLIED

Sulfadiazine 500 mg Tablets are white, unscored, capsule-shaped tablets, imprinted *E 757* and are available in bottles of 100 and 1000.

Storage: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

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

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured for

Sandoz Inc.

Princeton, NJ 08540

Manufactured by

Epic Pharma, LLC

Laurelton, NY 11413

OS7190

Rev. 10/08
MF0757REV10/08
MG #16918

SULFADIAZINE TABLETS USP, 500 MG X 100 TABLETS - LABEL

NDC 0185-0757-01

SulfADIAZine Tablets USP

500 mg

Rx only

100 Tablets

Sandoz

Exp. Date:
No Varnish

Lot No.:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

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

Rev. 10/08
L2274

NDC 0185-0757-01

**SulfADIAZine
Tablets USP**

500 mg



Rx only

100 Tablets

SANDOZ

Each tablet contains:
Sulfadiazine 500 mg

Protect from moisture.

KEEP TIGHTLY CLOSED.

**KEEP THIS AND ALL
MEDICATION OUT OF THE
REACH OF CHILDREN.**

Manufactured for
Sandoz Inc.
Princeton, NJ 08540

Manufactured by
Epic Pharma, LLC
Laurelton, NY 11413



N 0185-0757-015

TAXOL[®] (paclitaxel) INJECTION

(Patient Information Included)

Rx only

WARNING

TAXOL[®] (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H₂ antagonists. (See **DOSAGE AND ADMINISTRATION**.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

TAXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm³ and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.

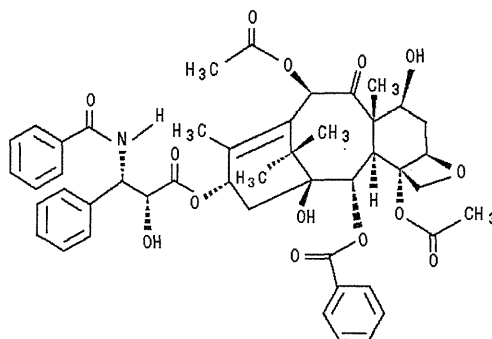
DESCRIPTION

TAXOL (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor[®] EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

*Cremophor[®] EL is the registered trademark of BASF Aktiengesellschaft.
Cremophor[®] EL is further purified by a Bristol-Myers Squibb Company proprietary process before use.

Paclitaxel is a natural product with antitumor activity. TAXOL (paclitaxel) is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for paclitaxel is 5 β ,20-Epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula C₄₇H₅₁NO₁₄ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216–217° C.

CLINICAL PHARMACOLOGY

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Following intravenous administration of TAXOL, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions of TAXOL at dose levels of 135 and 175 mg/m² were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table.

TABLE 1
SUMMARY OF PHARMACOKINETIC PARAMETERS—MEAN VALUES

| Dose (mg/m ²) | Infusion Duration (h) | N (patients) | C _{max} (ng/mL) | AUC _(0-∞) (ng•h/mL) | T-HALF (h) | CL _T (L/h/m ²) |
|------------------------------|--------------------------|-----------------|-----------------------------|-----------------------------------|---------------|--|
| 135 | 24 | 2 | 195 | 6300 | 52.7 | 21.7 |
| 175 | 24 | 4 | 365 | 7993 | 15.7 | 23.8 |
| 135 | 3 | 7 | 2170 | 7952 | 13.1 | 17.7 |
| 175 | 3 | 5 | 3650 | 15007 | 20.2 | 12.2 |

C_{max}=Maximum plasma concentration

AUC_(0-∞)=Area under the plasma concentration-time curve from time 0 to infinity

CL_T=Total body clearance

It appeared that with the 24-hour infusion of TAXOL, a 30% increase in dose (135 mg/m² vs 175 mg/m²) increased the C_{max} by 87%, whereas the AUC_(0-∞) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{max} and AUC_(0-∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24-hour infusion of TAXOL, ranged from 227 to 688 L/m², indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15 to 135 mg/m² given by 1-hour infusions (n=15), 30 to 275 mg/m² given by 6-hour infusions (n=36), and 200 to 275 mg/m² given by 24-hour infusions (n=54) in Phase 1 and 2 studies. Values for CL_T and volume of distribution were consistent with the findings in the Phase 3 study. The pharmacokinetics of TAXOL in patients with AIDS-related Kaposi's sarcoma have not been studied.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89 to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15 to 275 mg/m² doses of TAXOL as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m² dose of radiolabeled TAXOL as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α-hydroxypaclitaxel, accounted for

the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6 α -hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to 2 minor metabolites, 3'-*p*-hydroxypaclitaxel and 6 α , 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6 α -hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17 α -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 α -hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See **PRECAUTIONS: Drug Interactions.**)

The disposition and toxicity of paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin ≤ 2 times upper limit of normal (ULN) administered 175 mg/m² was increased, but with no apparent increase in the frequency or severity of toxicity. In 5 patients with serum total bilirubin > 2 times ULN, there was a statistically nonsignificant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m²), but no observed increase in plasma exposure. (See **PRECAUTIONS: Hepatic** and **DOSAGE AND ADMINISTRATION.**) The effect of renal dysfunction on the disposition of paclitaxel has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Ovarian Carcinoma

First-Line Data: The safety and efficacy of TAXOL followed by cisplatin in patients with advanced ovarian cancer and no prior chemotherapy were evaluated in 2, Phase 3 multicenter, randomized, controlled trials. In an Intergroup study led by the European Organization for Research and Treatment of Cancer involving the Scandinavian Group NOCOVA, the National Cancer Institute of Canada, and the Scottish Group, 680 patients with Stage II_{B-C}, III, or IV disease (optimally or non-optimally debulked) received either TAXOL 175 mg/m² infused over 3 hours followed by cisplatin 75 mg/m² (Tc) or

cyclophosphamide 750 mg/m² followed by cisplatin 75 mg/m² (Cc) for a median of 6 courses. Although the protocol allowed further therapy, only 15% received both drugs for 9 or more courses. In a study conducted by the Gynecological Oncology Group (GOG), 410 patients with Stage III or IV disease (>1 cm residual disease after staging laparotomy or distant metastases) received either TAXOL 135 mg/m² infused over 24 hours followed by cisplatin 75 mg/m² or cyclophosphamide 750 mg/m² followed by cisplatin 75 mg/m² for 6 courses.

In both studies, patients treated with TAXOL (paclitaxel) in combination with cisplatin had significantly higher response rate, longer time to progression, and longer survival time compared with standard therapy. These differences were also significant for the subset of patients in the Intergroup study with non-optimally debulked disease, although the study was not fully powered for subset analyses (TABLES 2A and 2B). Kaplan-Meier survival curves for each study are shown in FIGURES 1 and 2.

TABLE 2A
EFFICACY IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA STUDIES

| | Intergroup (non-optimally debulked subset) | | GOG-111 | |
|---|---|-------------------------------------|--|-------------------------------------|
| | T175/3 ^a c75 (n=218) | C750 ^a c75 (n=227) | T135/24 ^a c75 (n=196) | C750 ^a c75 (n=214) |
| • Clinical Response ^b | (n=153) | (n=153) | (n=113) | (n=127) |
| —rate (percent) | 58 | 43 | 62 | 48 |
| —p-value ^c | | 0.016 | | 0.04 |
| • Time to Progression | | | | |
| —median (months) | 13.2 | 9.9 | 16.6 | 13.0 |
| —p-value ^c | | 0.0060 | | 0.0008 |
| —hazard ratio (HR) ^c | | 0.76 | | 0.70 |
| —95% CI ^c | | 0.62–0.92 | | 0.56–0.86 |
| • Survival | | | | |
| —median (months) | 29.5 | 21.9 | 35.5 | 24.2 |
| —p-value ^c | | 0.0057 | | 0.0002 |
| —hazard ratio ^c | | 0.73 | | 0.64 |
| —95% CI ^c | | 0.58–0.91 | | 0.50–0.81 |

^a TAXOL dose in mg/m²/infusion duration in hours; cyclophosphamide and cisplatin doses in mg/m².

^b Among patients with measurable disease only.

^c Unstratified for the Intergroup Study, Stratified for Study GOG-111.