

Trimetrexate glucuronate

Brand Name: Neutrexin

Drug Description

Trimetrexate glucuronate is an antiprotozoal dihydrofolate reductase inhibitor. [1] It is also classed as an antineoplastic. [2]

HIV/AIDS-Related Uses

Trimetrexate glucuronate was approved by the FDA on December 17, 1993 for use in the treatment of moderate-to-severe *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia (PCP) in AIDS patients. Trimetrexate is not considered the drug of choice for treatment of PCP, but has been recommended as an alternative in patients who are intolerant of, or whose disease is refractory to, sulfamethoxazole-trimethoprim or in whom such therapy is contraindicated.[3]

Leucovorin must be given concurrently with trimetrexate to prevent potential serious side effects (bone marrow depression, oral and gastrointestinal mucosal ulceration) that can occur if trimetrexate is given alone.[4]

Non-HIV/AIDS-Related Uses

Trimetrexate glucuronate is used in the treatment of moderate-to-severe PCP in immunocompromised patients who are intolerant of, or whose disease is refractory to, co-trimoxazole therapy. Trimetrexate has also been used to treat head and neck, non-small cell lung, and pancreatic carcinomas. However, data for these uses are limited and more comparative, randomized clinical studies are required to define the role of trimetrexate in these conditions.[5]

Pharmacology

Trimetrexate is a competitive inhibitor of dihydrofolate reductase (DHFR) from bacterial, protozoan, and mammalian sources. Inhibition of DHFR results in the depletion of intracellular levels of tetrahydrofolate, a coenzyme required in the thymidylate biosynthetic pathway. Inhibition of folate-dependent formyltransferases and indirect inhibition of purine biosynthesis also occur, resulting in disruption of DNA, RNA, and protein

synthesis, with consequent cell death. At concentrations achieved with therapeutic doses of trimetrexate plus leucovorin, the selective transport of trimetrexate glucuronate, but not leucovorin, into *P. carinii* allows the concurrent administration of leucovorin to protect normal host cells from the cytotoxicity of trimetrexate without inhibiting the antifolate's inhibition of *P. carinii*. Thus, leucovorin must be co-administered with trimetrexate to provide a source of reduced folates necessary for normal cellular biosynthetic processes. Because *P. carinii* lacks the normal cellular carrier-mediated transport system, leucovorin is prevented from entering the organism.[6]

Trimetrexate is chemically related to methotrexate, but the drugs have different cellular entering mechanisms. In vitro, trimetrexate binds to the DHFR of *P. carinii* approximately 1500 times more potently than does trimethoprim, one of the two parts of co-trimoxazole therapy (usually of choice for treating PCP).[7]

Trimetrexate is lipid-soluble, distributing readily in ascitic fluid. The drug penetrates the cerebrospinal fluid (CSF) poorly, with CSF concentration less than 5% of the simultaneous serum concentration. Peak serum concentrations are approximately 3.7 mcg/ml to 4.4 mcg/ml after intravenous administration of a dose of 30 mg/m². It is not known if trimetrexate is distributed into breast milk, but breast-feeding is not recommended during trimetrexate therapy because of the potential for serious adverse effects in the nursing infant.[8]

Trimetrexate is in FDA Pregnancy Category D. No studies have been conducted to evaluate trimetrexate's effects on fertility, but during standard toxicity studies in mice and rats, degeneration of the testes and spermatocytes and arrest of spermatogenesis was observed. Trimetrexate can harm the fetus when administered to a pregnant woman, so women of childbearing potential should be counseled and use appropriate contraception to avoid becoming pregnant during trimetrexate therapy. Trimetrexate has been shown to be fetotoxic and teratogenic in rats and rabbits. These effects were observed at doses of 5% to 50% of the equivalent human therapeutic dose on a mg

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Pharmacology (cont.)

per square meter of body surface area basis. Teratogenic effects included skeletal, visceral, ocular, and cardiovascular abnormalities.[9]

Protein binding of trimetrexate in vitro has varied from 80% to 90%, depending on serum trimetrexate concentrations.[10] There is a suggestion of capacity-limited binding at concentrations greater than 1000 ng/ml.[11] Biphasic or triphasic elimination has been described, with a terminal half-life ranging from 11 to 20 hours. Elimination is primarily renal; active tubular secretion and tubular reabsorption are thought to be involved. However, only 10% to 20% of a dose is eliminated as unchanged drug within 48 hours. Fecal excretion of the parent compound is less than 6% of the dose over 48 hours.[12]

Adverse Events/Toxicity

Adverse effects seen with the use of trimetrexate glucuronate include neutropenia, anemia, fever, mouth sores or ulcers, skin rash and itching, and thrombocytopenia. Less severe adverse effects include confusion, nausea and vomiting, and stomach pain.[13]

Drug and Food Interactions

Concurrent use of bone marrow depressants or radiation therapy with trimetrexate may cause additive bone marrow depression; dosage reduction may be required when two or more bone marrow depressants, including radiation therapy, are used concurrently or consecutively. Cytochrome P450 inhibitors, hepatotoxic medications, or nephrotoxic medications should not be used concurrently with trimetrexate because hepatotoxic or nephrotoxic medications may decrease the clearance of trimetrexate, increasing the risk of trimetrexate toxicity.[14]

Contraindications

Risk-benefit assessment should be considered if the patient has any kind of bone marrow depression, hepatic function impairment, renal function impairment, or is hypersensitive to trimetrexate,

methotrexate, or leucovorin.[15] Trimetrexate glucuronate must be administered with concurrent leucovorin to avoid potentially serious or life-threatening toxicities.[16]

Clinical Trials

For information on clinical trials that involve Trimetrexate glucuronate, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Trimetrexate glucuronate AND HIV Infections.

Dosing Information

Mode of Delivery: Intravenous.[17]

Dosage Form: Trimetrexate glucuronate sterile lyophilized powder, 5-ml vials with equivalent of 25 mg trimetrexate and 30-ml vials with equivalent of 200 mg trimetrexate.[18]

Storage: Prior to reconstitution, trimetrexate glucuronate should be stored between 15 C and 30 C (69 F and 86 F) and protected from light.[19]

Chemistry

CAS Name: 2,4-Quinazolinediamine, 5-methyl-6-(((3,4,5-trimethoxyphenyl)amino)methyl)-, mono-D-glucuronate[20]

CAS Number: 82952-64-5[21]

Molecular formula:
C₁₉H₂₃N₅O₃.C₆H₁₀O₇[22]

C61.77%, H6.28%, N18.96%, O12.99% (base)[23]

Molecular weight: 563.56[24]

Physical Description: Trimetrexate D-glucuronate is a tan-colored solid.[25]

Trimetrexate glucuronate for injection is a pale greenish-yellow powder or cake.[26]

The reconstituted product will appear as a pale greenish-yellow solution.[27]

Trimetrexate glucuronate



Chemistry (cont.)

Stability: After initial reconstitution, trimetrexate solution is stable under refrigeration or at room temperature for up to 24 hours. The reconstituted solution should not be frozen. Unused portions should be discarded after 24 hours. A reconstituted solution that is further diluted with 5% dextrose is stable under refrigeration or at room temperature for up to 24 hours.[28]

Solubility: The solubility of trimetrexate glucuronate in water is greater than 50 mg/ml, whereas trimetrexate free base is practically insoluble in water (less than 0.1 mg/ml).[29]

Other Names

Trimetrexate D-glucuronate[30]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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