PRESCRIBING INFORMATION

Pr NEGGRAM®

(nalidixic acid tablets USP)

URINARY ANTIBACTERIAL

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Date of Preparation:
May 9, 2006

Submission Control No. 105766

s-a Version 1.0 dated

NAME OF DRUG

^{Pr}NegGram®
(nalidixic acid tablets U.S.P.)

THERAPEUTIC CLASSIFICATION

Urinary Antibacterial

ACTIONS AND CLINICAL PHARMACOLOGY

Nalidixic acid has marked antibacterial activity against gram negative bacteria including *Proteus mirabilis; P. morganii; P. vulgaris and P. rettgeri; Escherichia coli; Enterobacter (Aerobacter) and Klebsiella. Pseudomonas* strains are generally resistant to the drug.

Nalidixic acid acts by selectively inhibiting bacterial DNA synthesis. Nalidixic acid is bactericidal and is effective over the enire urinary pH range.

Conventional chromosomal resistance to nalidixic acid taken in full dosage has been reported to emerge in approximately 2 to 14% of patients during treatment; however, bacterial resistance to nalidixic acid has not been shown to be transferable via R factor.

Bacterial cross-resistance between nalidixic acid and other quinolone antimicrobials has been observed. Even in patients treated for prolonged periods, no fungal overgrowth has been reported during therapy with NegGram.

INDICATIONS AND CLINICAL USE

NegGram (nalidixic acid) is indicated for the treatment of patients with acute or chronic urinary tract infections due to one or more species of nalidixic acid-sensitive gram negative pathogenic organisms, in particular Proteus species, E. coli, Aerobacter and Klebsiella (disc sensitivity with the 30 μg disc is recommended). It is useful in mixed urinary tract infection when the nalidixic acid-sensitive gram negative rods predominate.

When urinary tract pathogens which are resistant to other types of antibacterial drugs are found to be sensitive to nalidixic acid, the use of NegGram should be considered.

CONTRAINDICATIONS

NegGram (nalidixic acid) is contraindicated in patients with known hypersensitivity to nalidixic acid, a history of convulsive disorders and in patients with porphyria. Until further experience is gained, the drug should not be administered to infants under 3 months of age.

WARNINGS

CNS effects, including brief convulsions, increased intracranial pressure and toxic psychosis have been reported with nalidixic acid therapy. Convulsive seizures have been reported with other drugs in this class. Therefore, NegGram (nalidixic acid) should be used with caution in patients with known or suspected CNS disorders such as cerebral arteriosclerosis or other factors which predispose to seizures (see Adverse Reactions). Quinolones may also cause central nervous system (CNS) stimulation which may lead to tremor, restlessness, lightheadedness, confusion and hallucinations. If these reactions occur in patients receiving nalidixic acid, the drug should be discontinued and appropriate measures instituted.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria and itching. Serious anaphylactoid reactions required immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway manangement, including intubation, should be administered as indicated.

PRECAUTIONS

Although prolonged treatment with NegGram (nalidixic acid) has been generally well tolerated, it is advisable to carry out blood counts and renal and liver function tests periodically if treatment is continued for more than two weeks.

NegGram should be used with caution in patients with liver disease or glucose-6-phosphate-dehydrogenase deficiency (see Adverse Reactions). While caution should be used in patients with severe renal failure, therapeutic concentrations of nalidixic acid in the urine, without increased toxicity due to drug accumulation in the blood, have been observed in patients on full dosage, with creatinine clearances as low as 2 to 8 mL/min. Howevere, it has been recommended that nalidixic acid not be used if the creatinine clearance is <10 mL/min.

Microorganisms may develop resistance to NegGram. It is also possible that resistant bacteria, not previously present or identified, may emerge. Conventional chromosomal resistance to NegGram taken in full dosage has been reported to emerge in approximately 2 to 14% of patients during treatment; however, bacterial resistance to NegGram has not been shown to be transferable via R factor. If bacterial resistance to NegGram emerges during treatment, it usually does so within 48 hours, permitting rapid change to another antimicrobial. Therefore, if the clinical response is unsatisfactory or if relapse occurs, cultures and sensitivity tests should be repeated. Underdosage with NegGram during initial treatment (with less than 4 g per day for adults) or during maintenance treatment (with less than 2 g per day for adults), may predispose a patient to emergence of bacterial resistance.(see Dosage and Administration). It should be recognized that apparent relapse or bacterial resistance may frequently be due to obstruction of the urinary tract.

Drug Interactions:

Active proliferation of the organism is a necessary condition for the antibacterial action of nalidixic acid and it is possible that the presence of bacteriostatic substances may inhibit its action. Such an effect has been demonstrated in vitro with nitrofurantoin, tetracycline and chloramphenicol.

Quinolones, including nalidixic acid, may enhance the effects of oral anticoagulants, warfarin or bishydroxycoumarin, by displacing significant amounts from serum albumin binding sites. When concomitant administration of these products cannot be avoided, daily measurements of prothrombin time or other suitable coagulation tests are essential.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been reports of theophylline-related side effects in patients on concomitant therapy with quinolones and theophylline. Therefore, monitoring of theophylline and plasma levels should be considered and dosage of theophylline adjusted, as required.,

Probenecid inhibits the tubular secretion of nalidixic acid and may reduce its efficacy in the treatment of urinary tract infections while increasing the risk of systemic side effects.

Serious gastrointestinal toxicity has been associated with the concomitant use of nalidixic acid and melphalan.

Interference with Laboratory Tests:

Nalidixic acid may cause false positive reactions in urine tests for glucose using copper reduction methods, such as Benedict's or Fehling's solution. Glucose specific tests based on glucose oxidase should therefore be used.

Incorrect values may be obtained for urinary 17-keto and ketogenic steroids in assays based on urinary vanillymandelic acid. An alternative test such as Porter-Silber for 17-hydroxycorticoids should therefore be used.

Usage in Children:

Nalidixic acid and related compounds have been shown to produce erosions in the cartilage of weight-bearing joints and other signs of arthropathy in immature animals of most species tested. Until the clinical significance of this finding is clarified, care should be exercised when prescribing nalidixic acid for pre-pubertal patients. If symptoms of arthralgia occur, treatment with nalidixic acid should be stopped.

Usage in Pregnancy:

The safety of nalidixic acid during pregnancy has not been established. Therefore, it should be used during pregnancy only if the potential benefits outweigh the potential risks especially during the first trimester (nalidixic acid crosses the placental barrier and has been shown to be taken up by growing cartilage in several animal species) and during the last month of pregnancy because of the potential risk for the neonate: exposure to maternal nalidixic acid *in utero* may lead to significant blood levels of nalidixic acid in the neonate immediately after birth.

Usage in Lactation:

Since nalidixic acid is excreted in breast milk, it is contraindicated during lactation.

Information for the Patient:

Patients should be advised that NegGram (nalidixic acid) may be taken with or without meals. Patients should be advised to drink fluids liberally and not take antacids within two hours of taking NegGram, as antacids may interfere with its absorption. Patients should be advised that quinolones may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reactions.

Since reversible photosensitiviy reactions have been reported in a small number of cases, patients should be cautioned to avoid direct sunlight while on NegGram therapy. Therapy should be discontinued if photosensitivity occurs.

Quinolones may cause dizziness and lightheadedness; therefore, patients should know how they react to NegGram before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised to avoid excessive caffeine intake, as quinolones may increase the effects of caffeine containing compounds.

ADVERSE REACTIONS

NegGram (nalidixic acid) is usually well tolerated. It is seldom necessary to discontinue treatment or to reduce the dosage.

Gastrointestinal:

Abdominal pain, nausea, vomiting and diarrhea.

Allergic:

Rash, pruritus, urticaria, eosinophilia, arthralgia with joint stiffness and swelling, and rarely, angioedema, anaphylactic shock and anaphylactoid reactions. Photosensitivity reactions consisting of erythema and bullae on exposed skin surfaces usually resolve completely in two weeks to two months after discontinuation of nalidixic acid; however, bullae may continue to appear with successive exposures to sunlight or with mild skin trauma for up to three months after discontinuation.

CNS:

Somnolence, drowsiness, weakness, headache, dizziness, vertigo and rare cases of paresthesia.

Toxic psychosis or brief convulsions have been reported rarely, usually following excessive doses. In general, the convulsions have occurred in patients with predisposing factors such as epilepsy or cerebral arteriosclerosis.

Intracranial hypertension with bulging anterior fontanel, papilledema and headache has occasionally been observed in infants and children receiving therapeutic doses of nalidixic acid. Isolated cases of sixth cranial nerve palsy have been reported. Although the mechanisms of these reactions are unknown, the signs and symptoms usually disappeared rapidly and without sequelae when treatment was discontinued.

Hematological:

Thrombocytopenia, leukopenia and hemolytic anemia (rare; observed in patients with and those without a deficiency in glucose-6-phosphate dehydrogenase activity). A single case of fatal acute immune hemolytic anemia has been reported, without a deficiency in glucose-6-phosphate dehydrogenase activity.

Ocular:

Reversible subjective visual disturbances without objective findings have occurred infrequently (generally with each dose during the first few days of treatment). Such disturbances include perceived overbrightness of lights, altered color perception, difficulty in focusing, decrease in visual acuity and diplopia. They usually disappear promptly on reduction of dosage or discontinuation of therapy.

Others:

Rarely, cholestasis and metabolic acidosis. Erythema Multiforme and Stevens-Johnson syndrome have been reported with nalidixic acid and other drugs in this class. A single case of non fatal pulmonary hypersensitivity to nalidixic acid has been reported in the literature.

SYMPTOMS AND TREATMENT OF OVERDOSE

Toxic psychosis, convulsions, increased intracranial pressure or metabolic acidosis may occur in patients taking more than the recommended dosage. Vomiting, nausea and lethargy may also occur following overdosage.

Reactions are likely to be short-lived because nalidixic acid is normally rapidly excreted. In the early phase following overdosage, gastric lavage is indicated. If systemic absorption has occurred, fluid intake should be promoted; supportive measures such as oxygen and means of artificial respiration should be available. Anticonvulsant therapy may be indicated in a severe case, although it has not been used in the few instances of overdosage that have been reported.

DOSAGE AND ADMINISTRATION

Adults:

The recommended dosage of NegGram (nalidixic acid) for initial therapy in adults is 1 g administered four times daily for one or two weeks (total daily dose 4 g). For prolonged therapy, the total daily dose may be reduced to 2 g after the initial treatment period. Underdosage during initial treatment may predispose to emergence of bacterial resistance. Adjustment of urinary pH is not necessary.

Children:

(See PRECAUTIONS regarding potential toxicity to cartilage).

Until further experience is gained, NegGram should not be administered to infants younger than three months. Dosage in children 12 years of age and under should be calculated on the basis of body weight. The recommended total daily dosage for initial therapy is 55 mg/kg/day, administered in four equally divided doses. For prolonged therapy, the total daily dose may be reduced to 33 mg/kg/day.

Patients with renal failure:

The normal dosage of nalidixic acid may be employed in patients with creatinine clearance of more than 20 mL/minute. Dosage should be halved in patients with creatinine clearance of 20 mL/minute or less.

NOTE:

In light of potential neurologic reactions, the recommended dose should not be increased except under the careful supervision of a physician.

AVAILABILITY

NegGram (nalidixic acid) is available as scored , yellow caplets, with “N” on one side of the score and “22” on the other, with the flying W on the reverse. Each caplet contains 500 mg nalidixic acid and as nonmedicinal ingredients cellulose (microcrystalline), methylcellulose, sodium lauryl sulfate, vegetable oil (hydrogenated) and yellow iron oxide. Available in bottles of 56 and 500 caplets.