

Gris-PEG® (griseofulvin ultramicronized) Tablets, USP 125 mg; 250 mg

DESCRIPTION

Gris-PEG® Tablets contain ultramicronized crystals of griseofulvin, an antibiotic derived from a species of *Penicillium*.

Each Gris-PEG® contains:

Active Ingredient: griseofulvin ultramicronized 125 mg.

Inactive Ingredients: colloidal silicon dioxide; lactose, magnesium stearate; methylcellulose; methylparaben; polyethylene glycol 400 and 8000; polyvinylpyrrolidone; and titanium dioxide.

OR

Active Ingredient: griseofulvin ultramicronized 250 mg. **Inactive Ingredients:** colloidal silicon dioxide; magnesium stearate; methylcellulose; methylparaben; polyethylene glycol 400 and 8000; povidone, sodium lauryl sulfate; and titanium dioxide.

ACTION

Microbiology—Griseofulvin is fungistatic with *in vitro* activity against various species of *Microsporum*, *Epidermophyton* and *Trichophyton*. It has no effect on bacteria or other genera of fungi.

Human Pharmacology—Following oral administration, griseofulvin is deposited in the keratin precursor cells and has a greater affinity for diseased tissue. The drug is tightly bound to the new keratin which becomes highly resistant to fungal invasions. The efficiency of gastrointestinal absorption of ultramicronized griseofulvin is approximately one and one-half times that of the conventional microsize griseofulvin. This factor permits the oral intake of two-thirds as much ultramicronized griseofulvin as the microsize form. However, there is currently no evidence that this lower dose confers any significant clinical differences with regard to safety and/or efficacy.

INDICATIONS

Gris-PEG® (griseofulvin ultramicronized) is indicated for the treatment of the following ringworm infections; tinea corporis (ringworm of the body), tinea pedis (athlete's foot), tinea cruris (ringworm of the groin and thigh), tinea barbae (barber's itch), tinea capitis (ringworm of the scalp), and tinea unguium (onychomycosis, ringworm of the nails), when caused by one or more of the following genera of fungi: *Trichophyton rubrum*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes*, *Trichophyton interdigitale*, *Trichophyton verrucosum*, *Trichophyton megnini*, *Trichophyton gallinae*, *Trichophyton crateriform*, *Trichophyton sulphureum*, *Trichophyton schoenleinii*, *Microsporum audouinii*, *Microsporum canis*, *Microsporum gypseum* and *Epidermophyton floccosum*. NOTE: Prior to therapy, the type of fungi responsible for the infection should be identified. The use of the drug is not justified in minor or trivial infections which will respond to topical agents alone. Griseofulvin is *not* effective in the following: bacterial infections, candidiasis (moniliasis), histoplasmosis, actinomycosis, sporotrichosis, chromoblastomycosis, coccidioidomycosis, North American blastomycosis, cryptococcosis (torulosis), tinea versicolor and nocardiosis.

CONTRAINDICATIONS

Two cases of conjoined twins have been reported since 1977 in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

This drug is contraindicated in patients with porphyria or hepatocellular failure and in individuals with a history of hypersensitivity to griseofulvin.

WARNINGS

Prophylactic Usage—Safety and efficacy of griseofulvin for prophylaxis of fungal infections have not been established.

Animal Toxicology—Chronic feeding of griseofulvin, at levels ranging from 0.5%-2.5% of the diet resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatoma in mice. Thyroid tumors, mostly adenomas but some carcinomas, have been reported in male rats receiving griseofulvin at levels of 2.0%, 1.0% and 0.2% of the diet, and in female rats receiving the two higher dose levels. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusion in this regard. In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Usage in Pregnancy—see CONTRAINDICATIONS section.

Animal Reproduction Studies—It has been reported in the literature that griseofulvin was found to be embryotoxic and teratogenic on oral administration to pregnant rats. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin. Suppression of spermatogenesis has been reported to occur in rats, but investigation in man failed to confirm this.

PRECAUTIONS

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hematopoietic, should be done. Since griseofulvin is derived from species of *Penicillium*, the possibility of cross-sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty. Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Lupus erythematosus or lupus-like syndromes have been reported in patients receiving griseofulvin. Griseofulvin decreases the activity of warfarin-type anticoagulants so that patients receiving these drugs concomitantly may require dosage adjustment of the anticoagulant during and after griseofulvin therapy. Barbiturates usually depress griseofulvin activity and concomitant administration may require a dosage adjustment of the antifungal agent. There have been reports in the literature of possible interactions between griseofulvin and oral contraceptives. The effect of alcohol may be potentiated by griseofulvin, producing such effects as tachycardia and flush.

ADVERSE REACTIONS

When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria, erythema multiforme-like drug reactions, and rarely, angioneurotic edema, and may necessitate withdrawal of therapy and appropriate countermeasures. Parosmia of the hands and feet have been reported rarely after extended therapy. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion, and impairment of performance of routine activities. Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs. When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

DOSAGE AND ADMINISTRATION

Accurate diagnosis of infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium. Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tinea capitis, 4 to 6 weeks; tinea corporis, 2 to 4 weeks; tinea pedis, 4 to 8 weeks; tinea unguium—depending on rate of growth—fingernails, at least 4 months; toenails, at least 6 months.

General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tinea pedis. In some forms of athlete's foot, yeasts and bacteria may be involved as well as fungi. Griseofulvin will not eradicate the bacterial or monilial infection. **Adults:** Daily administration of 375 mg (as a single dose or in divided doses) will give a satisfactory response in most patients with tinea corporis, tinea cruris, and tinea capitis. For those fungal infections more difficult to eradicate, such as tinea pedis and tinea unguium, a divided dose of 750 mg is recommended.

Pediatric Use: Approximately 3.3 mg per pound of body weight per day of ultramicronized griseofulvin is an effective dose for most pediatric patients. On this basis, the following dosage schedule is suggested: Children weighing 35 - 60 pounds - 125 mg to 187.5 mg daily. Pediatric patients weighing over 60 pounds - 187.5 mg to 375 mg daily. Children and infants 2 years of age and younger - dosage has not been established. Clinical experience with griseofulvin in children with tinea capitis indicates that a single daily dose is effective. Clinical relapse will occur if the medication is not continued until the infecting organism is eradicated.

HOW SUPPLIED

Gris-PEG® (griseofulvin ultramicronized) Tablets, 125 mg, white, scored, elliptical-shaped, embossed "Gris-PEG" on one side and "125" on the other. Gris-PEG® (griseofulvin ultramicronized) Tablets, 250 mg, white, scored, capsule-shaped, embossed "Gris-PEG" on one side and "250" on the other. The 125 mg strength is available in bottles of 100 (NDC 0884-0763-04). The 250 mg strength is available in bottles of 100, and 500 (NDC 0884-0773-04, and NDC 0884-0773-50 respectively). Both strengths are film-coated.

Rx ONLY

STORAGE

Store Gris-PEG® tablets at controlled room temperature 15°-30°C (59°-86°F) in tight, light-resistant containers.

Manufactured for:
PEDI-NOL PHARMACAL INC.
30 Banfi Plaza North
Farmingdale, NY 11735 U.S.A.

By:
NOVARTIS CONSUMER HEALTH INC.
Lincoln, NE 68501

Procedural Pain Is Often Undertreated In Infants and Children in the ED

Infants feel and remember painful experiences, and the intensity of their pain may be heightened.

BY DEEANNA FRANKLIN

Associate Editor

WASHINGTON — Not only do infants feel pain and remember painful experiences, but this pain may be magnified in the very young, said Robert M. Kennedy, M.D., at the first annual Advanced Pediatric Emergency Medicine Assembly.

"When I first started training 20 years ago, our 'improvement' was to decrease the number of people needed to hold down a child for a procedure by incorporating the use of Velcro," said Dr. Kennedy, of the pediatric emergency medicine department at St. Louis Children's Hospital.

"However, we know now that it is likely that an infant given the same stimulus as an older child actually perceives much more intense pain than that older child. So there may be a physiologic explanation as to why they cry louder and longer, and maybe harder," Dr. Kennedy said.

"We know now that by 24-26 weeks' gestation, about midway through the third trimester, nociceptive fibers from the ventroposterior thalamus have fully penetrated the primary somatosensory cortex. There's no question that when our babies are born, they certainly can perceive pain. It just astounds me that an infant's ability to feel pain was ever questioned," said Dr. Kennedy, also of Washington University in St. Louis.

A Tradition of Undertreating Pain

Dr. Kennedy suggested that underestimating infants' pain may have been a kind of coping mechanism for health care providers tasked with performing unpleasant but necessary procedures on children.

According to animal studies, infants are actually more sensitive to pain than adults, and their pain thresholds rise approximately 11-fold from birth to adulthood. Despite this finding, studies show that adults are more likely than children to receive effective pain medications, such as narcotics.

Both children and adults typically undergo painful routine procedures, such as placement of Foley and intravenous catheters without any anesthetic, he said.

The cause of a great source of confusion is that crying is accepted and expected behavior, Dr. Kennedy said, and health care providers tend to believe a child's crying reflects anxiety rather than pain. "Kids are expected to cry because they're anxious anyway," he said.

Consider whether the same injury in the examining clinician would likely be painful, he advised. If so, then the child is probably experiencing pain.

Pain also was traditionally undertreated because most clinicians feared the adverse effects of potent analgesics (such as morphine) and lacked the training to administer them, he added. In addition, there

was a lack of consensus on the best anesthetics to use.

"There's a tremendous fear of analgesic adverse effects, particularly with opioids," Dr. Kennedy explained. "Increasing new evidence suggests we should develop a fear of adverse effects, such as posttraumatic stress disorders, when no analgesic is used instead."

Although the recognition of procedural sedation's importance has come a long way, adults are still twice as likely as children to receive potent pain medication in emergency departments.

"We've done a lot in emergency medicine. We've certainly developed protocols and research studies into what's safe and what's effective, and in training our residents and our fellows in procedural sedation and analgesia. [However,] you still have to be of driving age or older to get a narcotic," he said.

Sedation and Pain Medicines

Ketamine may be the most commonly used drug for significant procedural sedation, and it may be the best for deep sedation. "It's the safest and, I think, our best choice," Dr. Kennedy said in an interview with this newspaper. "In addition to causing less respiratory depression than opioids, ketamine may block the later increased sensitivity to pain." A blockade of central sensitization or windup may result in less pain experienced after the procedure when ketamine is used. "This concept needs further investigation in the emergency setting," he contended.

Dr. Kennedy also mentioned numerous studies documenting the "ugly" side of ketamine—specifically, its psychotomimetic effects, which include schizophrenia-like symptoms such as hallucinations, delusions, illogical thinking, poverty of speech and thought, agitation, dissociation, memory lapses, withdrawal, disturbances of emotion and affect, and decreased motivation.

"These adverse effects are most noticeable during the recovery, but further confirmation of lack of persistence is needed," Dr. Kennedy said. He suggested possibly avoiding the drug in patients with a family history of psychosis, adding that the "genetics still need to be worked out."

Nitrous oxide, while less potent than ketamine, is another option, as are topical creams and ointments, which can mute the sting of intravenous starts or sutures. These numb the skin well but may take 30-60 minutes to achieve their full effect, so some health care providers may be reluctant to use them.

Dr. Kennedy favors using a 30-gauge needle to inject lidocaine, buffered to a neutral pH level, for procedures such as suturing. He suggests that toddlers or preschoolers sit in their caregiver's lap during procedures such as IV starts and suturing to help reduce anxiety. With the nearly painless administration of local

anesthetics combined with "positions of comfort," most young children don't need sedation.

Painful Memories

When it comes to the impact of early pain memories on child development, the jury is still out.

In his presentation, Dr. Kennedy described a study that showed neonates can remember pain. "Babies of diabetic mothers who had experienced heel punctures for blood glucose measurements, even when their skin was being cleaned with alcohol—a nonpainful stimulus—had more grimacing and were given higher estimates of pain by observers when blood was drawn for their newborn metabolic screen 1-2 days after the prior heel sticks," he said.

"And for the skin puncture, the same thing was true. So these babies had some process that enabled them to know, even when they were being wiped off with alcohol, that something noxious was about to happen," Dr. Kennedy said (JAMA 2002;288:857-61).

In another study, the authors proposed that not only do infants have a heightened awareness of pain because their descending inhibitory pain pathways are less developed, but that perinatal brain plasticity also increases the vulnerability to early adverse experiences, possibly leading to abnormal development and a predisposition to a range of self-destructive behaviors, including suicide and drug abuse (Biol. Neonate. 2000;77:69-82).

"Infants at their 4- to 6-month immunizations cried longer, grimaced a lot more, and showed much more distress if they had been circumcised without local anesthetic, as opposed to noncircumcised infants," Dr. Kennedy said. "And this is 4-6 months after a painful procedure. There's something going on here, even in a newborn, that we're having a hard time figuring out how to measure, but it certainly is something we need to take into account."

The Current Trend

Children are much more likely now to receive procedural sedation because of improvements in training over the last 10-15 years, and the trend needs to continue. "Anesthetics cause a little bit of vasoconstriction, but you get used to it," he said. Greater public awareness also has caused more caregivers to ask for sedation or local anesthetics.

Dr. Kennedy contended that the pendulum may have swung too far in the direction of sedation in his emergency department. Distraction is a nonpharmacologic technique worth trying, he suggested. Self-reports of pain intensity have been lower after the patient was distracted.

"When we can provide effective painless local anesthesia, we should help kids with their own coping mechanisms," he said. "This is not only safer, but it leads to greater satisfaction for many children and their parents and uses fewer ED resources." ■