

POLICY & PRACTICE

Mandating HPV Vaccination

Under a proposal gaining momentum in Michigan, vaccination against human papillomavirus (HPV) would be required for all girls entering the sixth grade beginning next school year. Two pieces of legislation introduced in the Michigan state senate last month would require the HPV vaccine to be added to the roster of required immunizations for the state's public and private schools. While the vaccine would be required, parents could choose to opt out for medical, religious, or philosophical reasons. If this legislation is passed by the

legislature and signed by the governor, Michigan would be the first state to require the HPV vaccine for school entry, according to state Sen. Beverly Hammerstrom, a Republican, who introduced the bills. "Recent studies have shown that cervical cancer may be one of the few cancers that is actually preventable. This new vaccine will serve as our most effective tool in the fight against cervical cancer," she said in a statement. "For the first time in history, we have an opportunity to finally eliminate this deadly disease." The bills have the support of all of the women in

the Michigan senate, according to Sen. Hammerstrom. The FDA approved one HPV vaccine (Gardasil) for girls and women aged 9-26 in June. Also in June, the Advisory Committee on Immunization Practices, which advises officials at the Centers for Disease Control and Prevention, recommended routine vaccination in girls 11-12 years old and permissive use in individuals aged 9-26.

Exclusivity Data Not Reaching Doctors

Results from a huge number of trials undertaken specifically to investigate dosing, safety, or efficacy of pharmaceuticals in children are not reaching clinicians, re-

searchers from the FDA and the Duke Clinical Research Institute reported. They examined studies conducted from 1998 to 2004 by manufacturers seeking patent extensions under the FDA's pediatric exclusivity rule. During that time, 253 studies were submitted to the FDA—125 evaluating efficacy, 51 on multidose pharmacokinetics, 34 on single-dose pharmacokinetics, and 43 on safety. For half (127), the results indicated a label change, but only 113 were published. Studies that showed efficacy or had results that gave rise to a positive labeling change were more likely to be published, wrote the authors in the Sept. 13 issue of the *Journal of the American Medical Association*. Of 100 trials associated with a key labeling change—that is, one that would show substantive dosing changes, new safety information, or lack of efficacy in phase III—only 37 were published. While the pediatric exclusivity rule has promoted new research, "the research has not been consistently disseminated into the peer-reviewed medical literature"—a crucial step to educating and notifying the prescriber, said the authors.

Gaps in Mental Health Knowledge

Clinicians now have better information on the short-term efficacy of medications for children with mental illnesses and behavioral problems, but there is a need for more evidence on the long-term impact and safety of these therapies, according to a report from the American Psychological Association. More research also needs to be conducted in practice settings to show the benefits of therapies under real-life conditions, the report said. The report, which was produced by the APsA Working Group on Psychotropic Medications for Children and Adolescents, provides a review of the current literature on the use, sequencing, and integration of psychotropic medications and psychosocial interventions in children and adolescents. The group found that evidence for treatment efficacy is "uneven" across disorders, with most of the research attention focused on childhood ADHD, adolescent depression, and anxiety disorders. But there is less information on treatment efficacy available for some of the most severe conditions, including bipolar disorder and schizophrenia, the report noted.

FDA Brings on New Ethicist

Dr. Robert M. Nelson, who has served as the chairman of the Food and Drug Administration's Pediatric Advisory Committee for the last 2 years, is joining the agency full-time as an ethicist in the Office of Pediatric Therapeutics. Dr. Nelson is an associate professor of anesthesiology and critical care at the Children's Hospital of Philadelphia; he will keep his faculty appointments at the University of Pennsylvania, Philadelphia. Dr. Nelson is also a former chairman of the American Academy of Pediatrics' Committee on Bioethics. At the Office of Therapeutics, he will guide the agency on issues related to pediatric clinical trials and products that may have an impact on children. "His expertise and experience further bolster our ability to ensure the highest level of scientific and ethical rigor in pediatric clinical research," said FDA acting commissioner Dr. Andrew von Eschenbach in a statement.

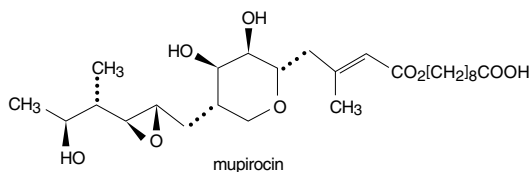
—From staff reports

CENTANY™

(MUPIROCIN OINTMENT), 2%

DESCRIPTION

Each gram of Centany (mupirocin ointment), 2% contains 20 mg mupirocin in a soft white ointment base consisting of castor oil, oleyl alcohol, hard fat (Softisan® 378) and propylene glycol monostearate. Mupirocin is a naturally occurring antibiotic. The chemical name is (E)-(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2-H-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. The molecular formula of mupirocin is C₂₆H₄₄O₉ and the molecular weight is 500.63. The chemical structure is:



CLINICAL PHARMACOLOGY

Following the application of Centany (mupirocin ointment), 2% to a 400 cm² area on the back of 23 healthy volunteers once daily for 7 days, the mean (range) cumulative urinary excretion of monic acid over 24 hrs following the last administration was 1.25% (0.2% to 3.0%) of the administered dose of mupirocin. The monic acid concentration in urine collected at specified intervals for 24 hrs on Day 7 ranged from <0.050 to 0.637 μg/mL.

Microbiology: Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. Its spectrum of activity includes gram-positive bacteria. It is also active, *in vitro* only, against certain gram-negative bacteria. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin does not demonstrate cross-resistance with other classes of antimicrobial agents.

When mupirocin resistance occurs, it results from the production of a modified isoleucyl-tRNA synthetase or the acquisition, by genetic transfer, of a plasmid mediating a new isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC > 500 mcg/mL) has been reported in increasing numbers of isolates of *Staphylococcus aureus* and with higher frequency in coagulase-negative staphylococci. Methicillin resistance and mupirocin resistance commonly occur together in *Staphylococcus aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical administration. However, the minimum bactericidal concentration (MBC) against relevant pathogens is generally eight-fold to thirty-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of wound secretions on the MICs of mupirocin has not been determined.

Mupirocin has been shown to be active against susceptible strains of *Staphylococcus aureus* and *Streptococcus pyogenes*, both *in vitro* and in clinical studies. (See INDICATIONS AND USAGE.)

INDICATIONS AND USAGE

Centany (mupirocin ointment), 2% is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus* and *Streptococcus pyogenes*.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components.

WARNINGS

Centany (mupirocin ointment), 2% is not for ophthalmic use.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of Centany (mupirocin ointment), 2%, treatment should be discontinued and appropriate alternative therapy for the infection instituted.

As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Centany (mupirocin ointment), 2% is not formulated for use on mucosal surfaces. Centany (mupirocin ointment), 2% is not intended for nasal use.

Information for Patients: Use this medication only as directed by your healthcare provider. It is for external use only. Avoid contact with the eyes. The medication should be stopped and your healthcare practitioner contacted if irritation, severe itching or rash occurs. If impetigo has not improved in 3 to 5 days, contact your healthcare practitioner.

OrthoNeutrogena

Rx only For Dermatologic Use

Drug Interactions: The effect of the concurrent application of Centany (mupirocin ointment), 2% and other drug products is unknown.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential of mupirocin have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium *in vitro* and *in vivo* did not indicate a potential for genotoxicity: rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Reproduction studies were performed in male and female rats with mupirocin administered subcutaneously at doses up to 14 times the human topical dose (approximately 60 mg mupirocin/day) on a mg/m² basis and revealed neither evidence of impaired fertility nor impaired reproductive performance attributable to mupirocin.

Pregnancy

Teratogenic Effects.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 22 and 43 times, respectively, the human topical dose (approximately 60 mg mupirocin per day) on a mg/m² basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Centany (mupirocin ointment), 2% is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Centany (mupirocin ointment), 2% have been established in the age range of 2 months to 16 years. Use of Centany (mupirocin ointment), 2% in these age groups is supported by evidence from adequate and well-controlled studies of Centany (mupirocin ointment), 2% in impetigo in pediatric patients studied as a part of the pivotal clinical trials. (See CLINICAL STUDIES.)

ADVERSE REACTIONS

The following local adverse reactions have been reported in connection with the use of Centany (mupirocin ointment), 2%: application site reactions and pruritus, each in 1% of patients; contact dermatitis and furunculosis, each in 0.7% of patients; and exfoliative dermatitis and rash, each in 0.3% of patients.

DOSAGE AND ADMINISTRATION

A small amount of Centany (mupirocin ointment), 2% should be applied to the affected area three times daily. The area treated may be covered with a gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

CLINICAL STUDIES

The efficacy of topical Centany (mupirocin ointment), 2% in impetigo was tested in one study. Patients with impetigo were randomized to receive either Centany (mupirocin ointment, 2%) or Bactroban® Ointment (mupirocin ointment, 2%) t.i.d. for 7 days. Clinical efficacy rates at the follow-up visit (one week after end of therapy) in the evaluable populations (adults and pediatric patients included) were 94% for Centany (mupirocin ointment, 2%) (n=233) and 95% for Bactroban® Ointment (mupirocin ointment, 2%) (n=242). Pathogen eradication rates at follow-up for both medications were 98%.

Pediatrics

There were 413 pediatric patients aged 2 months to 15 years in the clinical study described above. Clinical efficacy rates at follow-up in the evaluable populations were 93% for Centany (mupirocin ointment, 2%) (n=199) and 95% for Bactroban® Ointment (mupirocin ointment, 2%) (n=214).

HOW SUPPLIED

Centany (mupirocin ointment), 2% is supplied in 15 gram (NDC 0062-1610-01) and 30 gram (NDC 0062-1610-03) tubes.

Store at controlled room temperature 20° to 25°C (68° to 77°F).

OrthoNeutrogena

Distributed by: OrthoNeutrogena, Division of Ortho-McNeil Pharmaceutical, Inc. Skillman, New Jersey 08558 ©OMP 2003 Issued May, 2003 Printed in USA

635-10-686-1 [I473ONG-2]