

POLICY & PRACTICE

Influenza Update

Federal health officials are applauding the progress made in the first year of vaccinating children between the ages of 6 months and 23 months. As of mid-December, nearly 37% of children in that age group had received the vaccine, according to Julie Gerberding, M.D., director of the Centers for Disease Control and Prevention. “We’re considering this a very excellent coverage rate for the first year out,” Dr. Gerberding said at a press conference on the influenza vaccine. Dr. Gerberding also addressed charges that officials at the

Health and Human Services Department had inappropriately used state immunization grant funds to purchase additional nonpediatric influenza vaccine from Glaxo-SmithKline in Germany. The money was taken from there, Dr. Gerberding said, because it was the only money available at the time, and it was important to close the deal to procure more vaccine quickly. She added that the children’s vaccine money is only available for use by states annually through the end of the calendar year and that \$14 million still remained in the fund during the final days of December.

BRIEF SUMMARY

47002/Issued: December 2000

Protopic® (tacrolimus)

Ointment 0.03% Ointment 0.1%

FOR DERMATOLOGIC USE ONLY NOT FOR OPHTHALMIC USE

INDICATIONS AND USAGE: PROTOPICT Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated for short-term and intermittent long-term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.

CONTRAINDICATIONS: PROTOPICT Ointment is contraindicated in patients with a history of hypersensitivity to tacrolimus or any other component of the preparation.

PRECAUTIONS: General

Studies have not evaluated the safety and efficacy of PROTOPICT Ointment in the treatment of clinically infected atopic dermatitis. Before commencing treatment with PROTOPICT Ointment, clinical infections at treatment sites should be cleared.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi’s varicelliform eruption), treatment with PROTOPICT Ointment may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these infections, the balance of risks and benefits associated with PROTOPICT Ointment use should be evaluated.

In clinical studies, 33 cases of lymphadenopathy (0.8%) were reported and were usually related to infections (particularly of the skin) and noted to resolve upon appropriate antibiotic therapy. Of these 33 cases, the majority had either a clear etiology or were known to resolve. Transplant patients receiving immunosuppressive regimens (e.g., systemic tacrolimus) are at increased risk for developing lymphoma; therefore, patients who receive PROTOPICT Ointment and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, discontinuation of PROTOPICT Ointment should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see ADVERSE REACTIONS), PROTOPICT Ointment shortened the time to skin tumor formation in an animal photocarcinogenicity study (see Carcinogenesis, Mutagenesis, Impairment of Fertility). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

The use of PROTOPICT Ointment may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of PROTOPICT Ointment application and typically improve as the lesions of atopic dermatitis heal. With PROTOPICT Ointment 0.1%, 90% of the skin burning events had a duration between 2 minutes and 3 hours (median 15 minutes). Ninety percent of the pruritus events had a duration between 3 minutes and 10 hours (median 20 minutes). The use of PROTOPICT Ointment in patients with Netherton’s Syndrome is not recommended due to the potential for increased systemic absorption of tacrolimus. The safety of PROTOPICT Ointment has not been established in patients with generalized erythroderma.

Information for Patients (See patient package insert)

Patients using PROTOPICT Ointment should receive the following information and instructions:

- 1. Patients should use PROTOPICT Ointment as directed by the physician. PROTOPICT Ointment is for external use only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.
- 2. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using PROTOPICT Ointment.
- 3. Patients should not use this medication for any disorder other than that for which it was prescribed.
- 4. Patients should report any signs of adverse reactions to their physician.
- 5. Before applying PROTOPICT Ointment after a bath or shower, be sure your skin is completely dry.

Drug Interactions

Formal topical drug interaction studies with PROTOPICT Ointment have not been conducted. Based on its minimal extent of absorption, interactions of PROTOPICT Ointment with systemically administered drugs are unlikely to occur but cannot be ruled out. The concomitant administration of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes. Reproductive toxicology studies were not performed with topical tacrolimus.

Pregnancy:

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of topically administered tacrolimus in pregnant women. The experience with PROTOPICT Ointment when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy. There are no adequate and well-controlled studies of systemically administered tacrolimus in pregnant women. Tacrolimus is transferred across the placenta. The use of systemically administered tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. PROTOPICT Ointment should be used during pregnancy only if the potential benefit to the mother justifies a potential risk to the fetus.

Nursing Mothers

Although systemic absorption of tacrolimus following topical applications of PROTOPICT Ointment is minimal relative to systemic administration, it is known that tacrolimus is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tacrolimus, 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.

Pediatric Use

PROTOPICT Ointment 0.03% may be used in pediatric patients 2 years of age and older. Two phase 3 pediatric studies were conducted involving 606 patients 2-15 years of age: one 12-week randomized vehicle-controlled study and one open-label, 1 year, long-term safety study. Three hundred and thirty (330) of these patients were 2 to 6 years of age.

The most common adverse events associated with PROTOPICT Ointment application in pediatric patients were skin burning and pruritus (see ADVERSE REACTIONS). In addition to skin burning and pruritus, the less common events (< 5%) of varicella zoster (mostly chicken pox), and vesiculobullous rash were more frequent in patients treated with PROTOPICT Ointment 0.03% compared to vehicle. In the long-term 1 year safety study involving 255 pediatric patients using PROTOPICT Ointment, the incidence of adverse events, including infections, did not increase with increased duration of study drug exposure or amount of ointment used. In 491 pediatric patients treated with PROTOPICT Ointment, 3(0.6%) developed eczema herpeticum. Since the safety and efficacy of PROTOPICT Ointment have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended.

Geriatric Use

Twenty-five (25) patients ≥ 65 years old received PROTOPICT Ointment in phase 3 studies. The adverse event profile for these patients was consistent with that for other adult patients.

ADVERSE REACTIONS:

No phototoxicity and no photoallergenicity was detected in clinical studies of 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study.

In three randomized vehicle-controlled studies and two long-term safety studies, 655 and 571 patients respectively, were treated with PROTOPICT Ointment.

The following table depicts the adjusted incidence of adverse events pooled across the 3 identically designed 12-week studies for patients in vehicle, PROTOPICT Ointment 0.03%, and PROTOPICT Ointment 0.1% treatment groups, and the unadjusted incidence of adverse events in two one year long-term safety studies, regardless of relationship to study drug.

Incidence Of Treatment Emergent Adverse Events

	12-Week, Randomized, Double-Blind, Phase 3 Studies 12-Week Adjusted Incidence Rate (%)				Open-Label Studies (up to 1 year) 0.1% Tacrolimus Ointment Incidence(%)	
	Adult		Pediatric		Adult	Pediatric
	Vehicle n=212	0.03% Tacrolimus Ointment n=210	0.1% Tacrolimus Ointment n=209	Vehicle n=116	0.03% Tacrolimus Ointment n=316	n=255
Skin Burning <sup>1</sup>	26	46	58	29	43	47
Pruritus <sup>2</sup>	37	46	46	27	41	25
Flu-like symptoms <sup>3</sup>	19	23	31	25	28	22
Allergic Reaction	8	12	6	8	4	22
Skin Erythema	20	25	28	13	12	12
Headache <sup>4</sup>	11	20	19	8	5	10
Skin Infection	11	12	5	14	10	11
Fever	4	4	1	13	21	2
Infection	1	1	2	9	7	14
Cough Increased	2	1	1	14	18	3
Asthma	4	6	4	6	6	5
Herpes Simplex	4	4	4	2	0	12
Eczema Herpeticum	0	1	1	0	2	0
Pharyngitis	3	3	4	11	6	5
Accidental Injury	4	3	6	3	6	4
Pustular Rash	2	3	4	3	2	6
Folliculitis <sup>5</sup>	1	6	4	0	2	11
Rhinitis	4	3	2	2	6	5

Teens Delaying Sexual Activity

Sexual activity among younger teenagers declined significantly between 1995 and 2002, while use of contraception increased, according to a study by the Centers for Disease Control and Prevention. Among never-married teenage girls aged 15-17 years, 30% of those surveyed in 2002 had ever had intercourse, compared with 38% in 1995. Among boys who were the same age, the percentage dropped from 43% in 1995 to 31% in 2002. The numbers were more mixed among teens aged 18-19; the percentage of boys in that group who had ever had sex dropped from 75% to 64%, but the percentage

among the girls actually went from 68% to 69%. More than three-quarters used contraception when they began having intercourse. “More teenagers are avoiding or postponing sexual activity, which can lead to sexually transmitted diseases, unwanted pregnancy, or emotional and societal responsibilities for which they are not prepared,” according to a statement by the Department of Health and Human Services.

Abstinence Education Evaluated

Federally funded abstinence-only education programs contain errors and misinformation on the effectiveness of condoms, the risks of abortion, and the transmission of disease, according to a recent report from Rep. Henry Waxman (D-Calif.). The report reviewed school-based sex education curricula used by federally funded programs. For example, one curriculum states that data do not support

Continued on following page

FDA Issues Warning for ADHD Drug

The Food and Drug Administration has issued a new warning for atomoxetine HCl concerning the potential for severe liver injury. The drug, indicated for the treatment of attention-deficit hyperactivity disorder in adults and children, has been available since 2002.

Two cases of severe liver injury were reported in a teenager and an adult who had taken atomoxetine (Strattera) for several months. Both patients recovered normal liver function after discontinuing the medication.

The revised labeling will state that severe liver injury may progress to liver failure, which can result in death or the need for an organ transplant. It will point out that because of the possible underreporting of adverse events, the actual number of cases of liver injury is unknown, and atomoxetine should be discontinued in patents who have developed jaundice or have laboratory evidence of liver injury.

Eli Lilly & Co., manufacturer of the medication, will issue “Dear Healthcare Provider” letters to alert prescribers to this new warning. “Our thorough review of the clinical trial and real-world data indicate that the benefit-risk profile for Strattera is positive,” Douglas Kelsey, M.D., a pediatrician and clinical research physician with Eli Lilly, said in a written statement.

Patient package inserts will also carry information detailing the signs and symptoms of liver problems.

Reports of any adverse events associated with Strattera can be reported directly to Eli Lilly at 800-LillyRx, or to the FDA’s MedWatch program at 800-332-1088. MedWatch forms can be downloaded at <http://www.fda.gov/medwatch/safety/3500.pdf>. The agency can also take reports via fax at 800-FDA-0178, or by mail at MedWatch, HFD-410, FDA, 5600 Fishers Lane, Rockville, MD 20857.

—Deeanna Franklin

Otitis Media	4	0	1	6	12	1	7
Sinusitis <sup>1</sup>	1	4	2	8	3	3	7
Diarrhea	3	3	4	2	5	4	6
Urticaria	3	3	6	1	1	5	5
Lack of Drug Effect	1	1	0	1	1	10	2
Bronchitis	0	2	2	3	3	3	6
Vomiting	0	1	1	7	6	1	5
Maculopapular Rash	2	2	2	3	0	4	3
Rash <sup>2</sup>	1	5	2	4	2	2	5
Abdominal Pain	3	1	1	2	3	1	5
Fungal Dermatitis	0	2	1	3	0	2	6
Gastroenteritis	1	2	2	3	0	4	2
Alcohol Intolerance <sup>3</sup>	0	3	7	0	0	6	0
Acne <sup>4</sup>	2	4	7	1	0	2	4
Sunburn	1	2	1	0	0	4	4
Skin Disorder	2	2	1	1	4	1	4
Conjunctivitis	0	2	2	2	1	4	2
Pain	1	2	1	0	1	4	3
Vesiculobullous Rash <sup>5</sup>	3	3	2	0	4	2	2
Lymphadenopathy	2	2	1	0	3	2	3
Nausea	4	3	2	0	1	1	2
Skin Tingling <sup>1</sup>	2	3	8	1	2	2	1
Face Edema	2	2	1	2	1	3	1
Dysopsia <sup>1</sup>	1	1	4	0	0	1	4
Dry Skin	7	3	3	0	1	0	1
Hyperesthesia <sup>1</sup>	1	3	7	0	0	3	0
Skin Neoplasm							
Basalg <sup>1</sup>	1	1	1	0	0	2	3
Bac Pain <sup>1</sup>	0	2	2	1	1	3	1
Peripheral Edema	2	4	3	0	0	2	1
Varicella Zoster <sup>1</sup>							
Herpes Zoster <sup>1</sup>	0	1	0	0	5	1	3
Contact Dermatitis	1	3	3	3	4	1	1
Asthenia	1	2	3	0	0	2	1
Pneumonia	0	1	1	2	0	1	2
Eczema	2	2	2	0	0	3	0
Insomnia	3	4	3	1	1	1	0
Exfoliative Dermatitis	3	3	1	0	0	0	2
Dysmenorrhea	2	4	4	0	0	0	2
Periodontal Abscess	1	0	1	0	0	3	0
Myalgia <sup>1</sup>	0	3	2	0	0	1	0
Cyst <sup>1</sup>	0	1	3	0	0	0	0

<sup>1</sup> May be reasonably associated with the use of this drug product.

<sup>2</sup> Four cases of chicken pox in the pediatric 12-week study; 1 case of “zoster of the lip” in the adult 12-week study; 7 cases of chicken pox and 1 case of shingles in the open-label pediatric study; 2 cases of herpes zoster in the open-label adult study.

<sup>3</sup> Generally “warts.”

Other adverse events which occurred at an incidence greater than or equal to 1% in any clinical study include: alopecia, ALT or AST increased, anaphylactoid reaction, angina pectoris, angioedema, anorexia, anxiety, arrhythmia, arthralgia, arthritis, bilirubinemia, breast pain, cellulitis, cerebrovascular accident, cheilitis, chills, constipation, creatinine increased, dehydration, depression, dizziness, dyspnea, ear pain, ecchymosis, edema, epistaxis, exacerbation of untreated area, eye disorder, eye pain, furunculosis, gastritis, hernia, hyperglycemia, hypertension, hypoglycemia, hypoxia, laryngitis, leukocytosis, leukopenia, liver function tests abnormal, lung disorder, malaise, migraine, neck pain, neuritis, palpitations, paresthesia, peripheral vascular disorder, photosensitivity reaction, procedural complication, routine procedure, skin discoloration, sweating, taste perversion, tooth disorder, unintended pregnancy, vaginal moniliasis, vasodilatation, and vertigo.

OVERDOSAGE:

PROTOPICT Ointment is not for oral use. Oral ingestion of PROTOPICT Ointment may lead to adverse effects associated with systemic administration of tacrolimus. If oral ingestion occurs, medical advice should be sought.

DOSAGE AND ADMINISTRATION:

ADULT  
PROTOPICT Ointment 0.03% and 0.1%

Apply a thin layer of PROTOPICT Ointment 0.03% or 0.1% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis.

The safety of PROTOPICT Ointment under occlusion which may promote systemic exposure, has not been evaluated. **PROTOPICT Ointment 0.03% and 0.1% should not be used with occlusive dressings.**

PEDIATRIC  
PROTOPICT Ointment 0.03%

Apply a thin layer of PROTOPICT Ointment 0.03% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis. The safety of PROTOPICT Ointment under occlusion, which may promote systemic exposure, has not been evaluated. **PROTOPICT Ointment 0.03% should not be used with occlusive dressings.**

Rx only

Fujisawa Healthcare, Inc.  
Deerfield, IL 60015-2548  
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the claim that condoms help prevent the spread of sexually-transmitted diseases. In another case, a curriculum states that 5%-10% of women who undergo abortions will become sterile. "Serious and pervasive problems with the accuracy of abstinence-only curricula may help explain why these programs have not been shown to protect adolescents from sexually transmitted diseases and why youth who pledge abstinence are significantly less likely to make informed choices about precautions when they do have sex," the report said.

Fewer Children Are Smoking

Smoking among preteens is down—but the majority of children who do smoke are getting cigarettes from people they know, a national survey indicated, according to a research presented in the American Journal of Preventive Medicine (Am. J. Prev. Med. 2004; 27:267-76). The survey polled 58,911 children from grades 8 through 12, between 1997 and 2002. During this time period, the number of eighth graders who smoked every day dropped from 8.3% to 4.8%. Among 10th graders, the smoking rate dropped from 18.3% to 9.6%, while among 12th graders it fell from 23.3% to 14.5%. The number of kids smoking occasionally also dropped in all grades. There's a greater perception among children that cigarettes are dangerous, and there's more peer disapproval, said Lloyd D. Johnston, Ph.D., lead researcher of the report. Yet 65% of the children in each grade said they had friends or relatives who bought them cigarettes.

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AMA Tackles Children's Issues

The American Medical Association approved several measures at its 2004 inter-im meeting to protect the health and welfare of children.

Among the measures were one to encourage the development of a strong adolescent immunization program in the United States and one to support legislation that would prevent the over-the-counter sale of dextromethorphan products to individuals under the age of 18.

In a statement, the AMA opposed NASCAR's decision to advertise hard-liquor brands. In a national poll conducted by Reducing Underage Drinking

Through Coalitions Initiative, "63% of respondents agreed that marketing hard liquor on racecars sends the wrong message to children and teens about drinking and driving," said AMA President-elect J. Edward Hill, M.D.

Medicaid Prescription Drug Charges

The Medicaid program is being over-charged for prescription drugs, George M. Reeb testified to the House Energy and Commerce subcommittee on oversight and investigations. Mr. Reeb, assistant inspector general for the Centers for Medicare and Medicaid Audits at the Department of Health and Human Services,

said part of the problem is that states vary greatly in the reimbursement amounts they set for prescription drugs.

For example, "based on state data, we estimated that, overall, Medicaid could have saved as much as \$86.7 million in fiscal year 2001 if all 42 states had reimbursed at the same price as the lowest paying state for each of the drugs reviewed," he said in his testimony.

Among his recommendations is that states be provided with enhanced access to accurate wholesale pricing information and adopt other strategies to contain costs.

—Jennifer Silverman

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed DAPTACEL®

BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE: DAPTACEL® is indicated for active immunization against diphtheria, tetanus and pertussis in infants and children 6 weeks through 6 years of age (prior to seventh birthday).

Children who have had well-documented pertussis (culture positive for *B. pertussis* or epidemiologic linkage to a culture positive case) should complete the vaccination series with DT, some experts recommend including acellular pertussis vaccine as well. Although well-documented pertussis disease is likely to confer immunity, the duration of protection is unknown.<sup>1</sup>

CONTRAINDICATIONS: This vaccine is contraindicated in children and adults seven years of age and older. Hypersensitivity to any component of the vaccine is a contraindication to further administration.<sup>2</sup>

The following events after receipt of DAPTACEL® are contraindications to further administration of any pertussis-containing vaccine:<sup>2</sup>

• *An immediate anaphylactic reaction.* Because of uncertainty as to which component of the vaccine may be responsible, no further vaccination with diphtheria, tetanus or pertussis components should be carried out. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

• *Encephalopathy not attributable to another identifiable cause* (e.g., an acute, severe central nervous system disorder occurring within 7 days after vaccination and consisting of major alterations in consciousness, unresponsiveness or generalized or focal seizures that persist more than a few hours, without recovery within 24 hours). In such cases, DT vaccine should be administered for the remaining doses in the vaccination schedule.

The decision to administer or delay vaccination because of a current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. According to the ACIP, all vaccines can be administered to persons with mild illness such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness.<sup>1,2</sup> However, children with moderate or serious illness should not be immunized until recovered.<sup>4</sup>

Elective immunization procedures should be deferred during an outbreak of poliomyelitis because of the risk of provoking paralysis.<sup>5,6,7</sup>

WARNINGS: The stopper to the vial of this product contains dry natural latex rubber that may cause allergic reactions. If any of the following events occur within the specified period after administration of a whole-cell pertussis DTP or DTaP vaccine, providers and parents should evaluate the risks and benefits of subsequent doses of whole-cell pertussis DTP or DTaP vaccines:<sup>2</sup>

• Temperature of ≥40.5°C (105°F) within 48 hours, not attributable to another identifiable cause.

• Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.

• Persistent crying lasting ≥3 hours within 48 hours.

• Convulsions with or without fever within 3 days.

When a decision is made to withhold pertussis vaccine, immunization with DT vaccine should be continued.<sup>4</sup>

Because of the risk of hemorrhage, DAPTACEL® should not be given to children with any coagulation disorder, including thrombocytopenia, which would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Studies suggest that, when given whole-cell pertussis DTP vaccine, infants and children with a history of convulsions in first-degree family members have a 2.4-fold increased risk of neurologic events.<sup>8</sup> However, ACIP has concluded that a history of convulsions or other central nervous system disorders in parents or siblings is not a contraindication to pertussis vaccination and that children with such family histories should receive DTaP vaccines according to the recommended schedule.<sup>1,8,9</sup>

For infants or children at higher risk for seizures than the general population, an appropriate antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing an acellular pertussis component (including DAPTACEL®) and for the following 24 hours, to reduce the possibility of post-vaccination fever.<sup>2,9</sup>

Whether to administer DAPTACEL® to children with proven or suspected underlying neurologic disorders must be decided on an individual basis. An important consideration includes the current local incidence of pertussis. The ACIP has issued guidelines for such children.<sup>10</sup>

PRECAUTIONS: General: Care is to be taken by the health-care provider for the safe and effective use of this vaccine.

EpiPhrine Hydrochloride Solution (1:1,000), other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Health-care providers must be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.<sup>1,11</sup>

Before an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. The expected immune response to DAPTACEL® may not be obtained in immunosuppressed persons.<sup>1</sup> Pertussis-containing vaccines are not contraindicated in persons with HIV infection.<sup>1</sup>

IT IS EXTREMELY IMPORTANT WHEN A CHILD RETURNS FOR THE NEXT DOSE IN THE SERIES THAT THE PARENT OR GUARDIAN SHOULD BE QUESTIONED CONCERNING ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE OF VACCINE. (See CONTRAINDICATIONS AND ADVERSE REACTIONS.)

Drug Interactions: As with other intramuscular (I.M.) injections, use with caution in patients on anticoagulant therapy. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy is to be soon discontinued, it seems reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.<sup>4</sup>

If DAPTACEL® is administered to persons with an immunodeficiency disorder, on immunosuppressive therapy or after a recent injection of immune globulin, an adequate immunologic response may not occur.<sup>1,12</sup>

For information regarding simultaneous administration with other vaccines refer to DOSAGE AND ADMINISTRATION. If passive immunization is needed for tetanus or diphtheria prophylaxis, Tetanus Immune Globulin (Human) (TIG), or Diphtheria Antitoxin, if used, should be given in a separate site, with a separate needle and syringe.<sup>3</sup>

Carcinogenesis, Mutagenesis, Impairment of Fertility: DAPTACEL® has not been evaluated for its carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy Category C: Animal reproduction studies have not been conducted with DAPTACEL®. It is not known whether DAPTACEL® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. DAPTACEL® is NOT recommended for use in a pregnant woman.

Geriatric Use: This product is NOT recommended for use in adult populations.

Pediatric Use: SAFETY AND EFFECTIVENESS OF DAPTACEL® IN INFANTS BELOW 6 WEEKS OF AGE HAVE NOT BEEN ESTABLISHED. (See DOSAGE AND ADMINISTRATION.)

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE OR OLDER. Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) is to be used in individuals 7 years of age or older.

ADVERSE REACTIONS: Over 11,400 doses of DAPTACEL® have been administered to infants and toddlers in 6 clinical studies. In all, 3,694 children received a total of 3 doses and 476 children received 4 doses of DAPTACEL®.<sup>12,13,14,15,16,17,18</sup>

In the Sweden I Efficacy Trial, information on systemic and local reactions were recorded on a standard diary card kept for 14 days after each dose, and follow-up telephone calls were made 1 and 14 days after each injection. Telephone calls were made monthly to monitor the occurrence of severe events and/or hospitalizations for the 2 months after the last injection. As shown in Table 1, the 2,587 infants who enrolled to receive DAPTACEL® at 2, 4 and 6 months of age had similar rates of reactions within 24 hours as recipients of DT and significantly lower rates than infants receiving whole-cell pertussis DTP.<sup>12,13</sup>

One case of whole limb swelling and generalized symptoms, with resolution within 24 hours, was observed following dose 2 of DAPTACEL®. No episodes of anaphylaxis or encephalopathy were observed. No seizures were reported within 3 days of vaccination with DAPTACEL®. Over the entire study period, 6 seizures were reported in the DAPTACEL® group, 9 in the DT group and 3 in the whole-cell pertussis DTP group, for overall rates of 2.3, 3.5 and 1.4 per 1,000 vaccinees, respectively. One case of infantile spasms was reported in the DAPTACEL® group. There were no instances of invasive bacterial infection or death.<sup>12,13</sup>

Rates of serious adverse events that are less common than those reported in the Sweden I Efficacy Trial are not known at this time. Table 2 summarizes the safety results from the Phase II Study in Canada in children who were immunized at 2, 4, 6 and 17-18 months of age with DAPTACEL®, Local and systemic adverse events were consistently less common in DAPTACEL® recipients at 2, 4 and 6 months of age than in those who received whole-cell pertussis DTP vaccine. Following the fourth dose, the same trends were observed, except for rates of severe redness and swelling which did not differ between the 2 vaccine groups. Rates of local reactions of redness and swelling were increased following the fourth dose compared with the first 3 doses as was mild tenderness but there was no increase in severe tenderness.

TABLE 2<sup>13,16</sup>  
PERCENTAGE OF CHILDREN FROM PHASE II STUDY IN CANADA WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 72 HOURS OF VACCINATION WITH DAPTACEL® AND WHOLE-CELL PERTUSSIS DTP VACCINE AT 2, 4, 6 AND 17-18 MONTHS OF AGE

EVENT	Dose 1 (2 MONTHS)		Dose 2 (4 MONTHS)		Dose 3 (6 MONTHS)		Dose 4 (18 MONTHS)	
	DAPTACEL® N = 324	DTP® N = 108	DAPTACEL® N = 321	DTP® N = 106	DAPTACEL® N = 320	DTP® N = 104	DAPTACEL® N = 301	DTP® N = 97
Local								
Redness								
Any	12.7*	44.4	20.6*	57.5	22.2*	51.9	36.5*	55.7
≥10 mm	1.2*	13.9	7.8*	22.6	10.0*	17.3	27.9	36.1
≥35 mm	0.3*	3.7	0.3*	5.7	1.6	1.9	21.9	20.6
Swelling								
Any	4.3*	23.1	4.3*	32.1	4.7*	25.0	18.6*	28.9
≥10 mm	1.9*	15.7	2.2*	21.7	3.8*	14.4	15.9*	25.8
≥35 mm	0.3*	6.5	0*	5.7	0.9*	4.8	11.3	15.5
Tenderness <sup>†</sup>								
Any	10.2*	37.0	7.5*	51.9	8.8*	48.1	23.9*	86.6
Moderate + Severe	0.9*	13.0	1.2*	20.8	1.3*	17.3	3.0*	53.6
Severe	0*	4.6	0.3*	7.5	0*	4.8	0.3*	12.4
Systemic								
Fever <sup>‡</sup>								
Any	12.0*	43.7	7.7*	50.0	14.8*	53.2	14.5*	67.9
≥37.5°C (99.5°F)	0.7	1.9	0*	7.8	1.2*	11.7	1.9*	17.9
≥38°C (100.4°F)	0.3	0	0	1.0	0	1.1	0	0
Irritability <sup>§</sup>								
Any	41.0*	65.7	41.4*	68.9	40.9*	67.3	36.9*	79.4
Moderate + Severe	9.0*	18.5	6.9*	22.6	5.0*	22.1	5.0*	24.7
Severe	0	1.9	0.3	0	0	1.0	0	2.1
Anorexia <sup>  </sup>								
Any	16.0	22.2	9.0*	16.0	11.6*	23.1	17.6*	41.2
Moderate + Severe	1.5	3.7	0.9	2.8	1.3	1.9	2.0*	13.4
Severe	0	0	0.3	0	0	0	0	2.1
Drowsiness <sup>¶</sup>								
Any	43.2	52.8	21.8*	33.0	14.4*	32.7	13.3*	29.9
Moderate + Severe	7.7	8.3	2.8*	7.5	1.3	0	1.0*	6.2
Severe	0.3	0	0	0	0	0	0	0
Crying ≥3 Hours	0.6	0.9	0.3	0.9	0	1.0	0	1.0

N = Number of evaluable subjects    # DTP: whole-cell pertussis DTP vaccine (Aventis Pasteur Limited)    \* Significantly less reactogenic than whole-cell DTP vaccine, p<0.05    † Moderate = sustained dry crying with gentle pressure at injection site; Severe = cries when leg is moved    ‡ Temperature measurements were axillary    § Number of evaluable subjects for DAPTACEL®/DTP = 301/103, 296/102, 257/94 and 207/78 at 2, 4, 6 and 18 months, respectively    ¶ Moderate = more difficulty with settling, even with cuddling; Severe = persistent crying/screaming and inability to console    || Moderate = missed one or two feeds; Severe = little or no intake for more than two feeds    || Moderate = sleeping most of the time with difficulty arousing

The US Bridging Study was designed, in part, to assess the safety of DAPTACEL® in infants at 2, 4 and 6 months of age, with routinely recommended, concurrently given childhood vaccines (*Haemophilus influenzae* type b vaccine, OPV and hepatitis B). The incidence of redness, swelling, pain or tenderness at the injection site after each dose was 12.5% - 19.7%, 14.3% - 17.8% and, 15.9% - 30.5% respectively. Fever ≥38°C (100.4°F) was observed in 9.9% - 11.9% of subjects. One afebrile seizure occurred within 24 hours post dose 2 immunization (n = 321).<sup>13</sup>

Additional adverse reactions evaluated in conjunction with pertussis, diphtheria and tetanus vaccination are as follows:

• As with other aluminum-containing vaccines, a nodule may be palpable at the injection sites for several weeks. Sterile abscess formation at the site of injection has been reported.<sup>4,19</sup>

• Rarely, anaphylactic reactions (i.e., hives, swelling of the mouth, difficulty breathing, hypotension or shock) have been reported after receiving preparations containing diphtheria, tetanus and/or pertussis antigens.<sup>4</sup>

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although the evidence is inadequate to accept or reject a causal relation.<sup>20</sup>

A review by the Institute of Medicine (IOM) found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré syndrome.<sup>21</sup> The following illnesses have been reported as temporally associated with some vaccines containing tetanus toxoid: neurological complications<sup>22,23</sup> including cochlear lesion, brachial plexus neuropathies,<sup>24</sup> paralysis of the radial nerve,<sup>25</sup> paralysis of the recurrent nerve, accommodation paresis and EEG disturbances with encephalopathy (with or without permanent intellectual or motor function impairment).<sup>24,26</sup>

It is difficult to distinguish between the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.<sup>26</sup>

DOSAGE AND ADMINISTRATION: JUST BEFORE USE, SHAKE THE VIAL WELL, until a uniform, cloudy suspension results. WITHDRAW AND INJECT A 0.5 mL DOSE. Administer the vaccine intramuscularly (I.M.). In the children younger than 1 year (i.e., infants), the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is usually large enough for I.M. injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.<sup>1</sup>

Do NOT administer this product intravenously or subcutaneously.

Immunization Series: A 0.5 mL dose of DAPTACEL® is approved for administration as a 4 dose series at 2, 4 and 6 months of age, at intervals of 6-8 weeks and at 17-20 months of age. The customary age for the first dose is 2 months of age, but it may be given as early as 6 weeks of age and up to the seventh birthday. The interval between the third and fourth dose should be at least 6 months. It is recommended that DAPTACEL® be given for all doses in the series because no data on the interchangeability of DAPTACEL® with other DTaP vaccines exist. At this time, data are insufficient to establish the frequency of adverse events following a fifth dose of DAPTACEL® in children who have previously received 4 doses of DAPTACEL®.<sup>27</sup> DAPTACEL® may be used to complete the immunization series in infants who have received 1 or more doses of whole-cell pertussis DTP. However, the safety and efficacy of DAPTACEL® in such infants have not been fully demonstrated.<sup>2</sup>

PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DAPTACEL® OR ANY OTHER PERTUSSIS-CONTAINING VACCINES.<sup>3</sup> DAPTACEL® should not be combined through reconstitution or mixed with any other vaccine. If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use) should be given as needed to complete the series. Pre-term infants should be vaccinated according to their chronological age from birth.<sup>1</sup>

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with DAPTACEL®. There is no need to start the series over again, regardless of the time between doses.

STORAGE: DAPTACEL® should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date.

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