

Tiotropium Backed for COPD Exacerbation

BY ELIZABETH MEHCATIE

SILVER SPRING, MD. — A Food and Drug Administration advisory panel voted 11-1 that evidence from two studies provided enough evidence to support approval of a claim that treatment with the inhaled, dry-powder formulation of tiotropium reduces exacerbations in patients with chronic obstructive pulmonary disease.

At the meeting, 11 of the 12 members of the FDA's Pulmonary-Allergy Drugs Advisory Committee also voted that data from one of those studies, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, "adequately addressed" the potential safety signals of an increased risk of stroke and adverse cardiovascular outcomes associated with this product that have been recently identified in pooled

data and meta-analyses of tiotropium studies.

The dry-powder formulation of tiotropium is marketed as the Spiriva HandiHaler by Boehringer Ingelheim and Pfizer. It was approved in the United States in January 2004 for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and em-

physema. It is administered once daily; each inhalation contains a dose of 18 mcg of tiotropium, an anticholinergic.

The companies proposed that Spiriva be approved for reductions in COPD exacerbations based on the UPLIFT trial and the Veterans Affairs (VA) Exacerbations Trial. In the 6-month VA study, there were approximately 1,800 patients with COPD, most of whom were men and whose mean age was 68 years. The

Roflumilast Shows Promise For COPD

SAN DIEGO — Roflumilast improved lung function and prevented exacerbations in patients with chronic obstructive pulmonary disease with chronic bronchitis and severe airflow obstruction in a large 12-month randomized trial.

Results of the 1,568-patient, double-blind, placebo-controlled study known as the M2-125 trial indicate roflumilast is an important potential new advance in the treatment of a subset of patients with COPD, Dr. Andrew McIvor declared at the annual meeting of the American College of Chest Physicians.

Roflumilast (Daxas) is an investigational selective phosphodiesterase 4 inhibitor, a drug class that represents a novel approach to the treatment of COPD. Taken orally once daily, roflumilast targets the inflammation that's a hallmark of the disease, explained Dr. McIvor of St. Joseph's Healthcare Hamilton, Ont.

Participants in the eight-nation M2-125 trial had to have at least one documented moderate or severe COPD exacerbation during the year prior to enrollment. They were randomized to roflumilast 500 mcg once daily or placebo for 1 year, on top of background long-acting beta₂-agonist or short-acting anticholinergic therapy at stable doses, along with short-acting beta₂-agonists as needed. Long-acting anticholinergics and inhaled corticosteroids were not permitted.

The rate of moderate to severe COPD exacerbations requiring systemic steroids and/or treatment in a hospital was 1.21 cases per patient per year in the roflumilast group and 1.49 in controls, for a highly significant 18.5% relative risk reduction. Roflumilast showed a highly significant advantage, with a 33-mL increase in forced expiratory volume in 1 second (FEV₁) as compared to a 25-mL decrease with placebo over 12 months.

All-cause mortality was 3% per year in each group. Adverse events were mild in nature. The two that were more frequent in the roflumilast arm were diarrhea and weight loss, affecting 9% and 8% of patients, respectively. Nearly one-third of subjects in each treatment group withdrew from the study. The study was sponsored by Nycomed, formerly Altana Pharma, where Dr. McIvor is a consultant.

—Bruce Jancin

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed



Brief Summary: Please see package insert for full prescribing information.

INDICATIONS AND USAGE Adacel vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria and pertussis as a single dose in persons 11 through 64 years of age. The use of Adacel vaccine as a primary series, or to complete the primary series, has not been studied. Vaccination with Adacel vaccine may not protect all of vaccinated individuals.

CONTRAINDICATIONS A severe allergic reaction (e.g., anaphylaxis) after a previous dose of Adacel vaccine or any other tetanus toxoid, diphtheria toxoid or pertussis containing vaccine or any other component of this vaccine is a contraindication to vaccination with Adacel vaccine. Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered. (1,2) Encephalopathy within 7 days of a previous dose of a pertussis containing vaccine not attributable to another identifiable cause is a contraindication to vaccination with Adacel vaccine. (1-3)

WARNINGS Persons who experienced Arthus-type hypersensitivity reactions (e.g., severe local reactions associated with systemic symptoms) (4) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given emergency doses of tetanus toxoid containing vaccines more frequently than every 10 years, even if the wound is neither clean nor minor. (1,2,5,6) If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give Adacel vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks. (1-3) In the following situations, Adacel vaccine should generally be deferred:

- Moderate or severe acute illness with or without fever, until the acute illness resolves. (1,2)
- In adolescents, progressive neurologic disorder, including progressive encephalopathy, or uncontrolled epilepsy, until the condition has stabilized. (2)
- In adults, unstable neurologic condition (e.g., cerebrovascular events and acute encephalopathic conditions), until the condition has resolved or is stabilized. (1)

PRECAUTIONS General Before administration of Adacel vaccine, the patient's current health status and medical history should be reviewed in order to determine whether any contraindications exist and to assess the benefits and risks of vaccination. (See **CONTRAINDICATIONS** and **WARNINGS**.) Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents and equipment should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. If Adacel vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained.

Information for Vaccine Recipients and/or Parent or Guardian Before administration of Adacel vaccine, health-care providers should inform the vaccine recipient and/or parent or guardian of the benefits and risks. The health-care provider should inform the vaccine recipient and/or parent or guardian about the potential for adverse reactions that have been temporally associated with Adacel vaccine or other vaccines containing similar components. The health-care provider should provide the Vaccine Information Statements (VIS) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The vaccine recipient and/or parent or guardian should be instructed to report any serious adverse reactions to their health-care provider. Females of child-bearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy surveillance system to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with Adacel vaccine during pregnancy. If they are pregnant or become aware they were pregnant at the time of Adacel vaccine immunization, they are encouraged to contact directly or have their health-care professional contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE). Reporting adverse events after vaccination to VAERS (Vaccine Adverse Event Reporting System) by recipients and/or parents or guardian should be encouraged. The toll-free number for VAERS forms and information is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

Drug Interactions Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. (See **PRECAUTIONS, General**.) For information regarding simultaneous administration with other vaccines refer to the **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections.

Carcinogenesis, Mutagenesis, Impairment of Fertility No studies have been performed with Adacel vaccine to evaluate carcinogenicity, mutagenic potential, or impairment of fertility.

Pregnancy Category C Animal reproduction studies have not been conducted with Adacel vaccine. It is also not known whether Adacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adacel vaccine should be given to a pregnant woman only if clearly needed. Animal fertility studies have not been conducted with Adacel vaccine. The effect of Adacel vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies using pregnant rabbits. Animals were administered Adacel vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29. 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of Adacel vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study. (7)

Nursing Mothers It is not known whether Adacel vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Adacel vaccine is given to a nursing woman.

Pediatric Use Adacel vaccine is not indicated for individuals less than 11 years of age. (See **INDICATIONS AND USAGE**.) For immunization of persons 6 weeks through 6 years of age against diphtheria, tetanus and pertussis refer to manufacturers' package inserts for DTap vaccines.

Geriatric Use Adacel vaccine is not indicated for individuals 65 years of age and older. No data are available regarding the safety and effectiveness of Adacel vaccine in individuals 65 years of age and older as clinical studies of Adacel vaccine did not include participants in the geriatric population.

ADVERSE REACTIONS The safety of Adacel vaccine was evaluated in 4 clinical studies. A total of 5,841 individuals 11-64 years of age inclusive (3,393 adolescents 11-17 years of age and 2,448 adults 18-64 years) received a single dose of Adacel vaccine. The principal safety study was a randomized, observer-blind, active controlled trial that enrolled participants 11-17 years of age (Adacel vaccine N = 1,184; Td vaccine N = 792) and 18-64 years of age (Adacel vaccine N = 1,752; Td vaccine N = 573). Study participants had not received tetanus or diphtheria containing vaccines within the previous 5 years. Solicited local and systemic reactions and unsolicited adverse events were monitored daily for 14 days post-vaccination using a diary card. From days 14-28 post-vaccination, information on adverse events necessitating a medical contact, such as a telephone call, visit to an emergency room, physician's office or hospitalization, was obtained via telephone interview or at an interim clinic visit. From days 28 to 6 months post-vaccination, participants were monitored for unexpected visits to a physician's office or to an emergency room, onset of serious illness and hospitalizations. Information regarding adverse events that occurred in the 6 month post-vaccination time period was obtained from the participant via telephone. Approximately 96% of participants completed the 6-month follow-up evaluation. In the concomitant vaccination study with Adacel and Hepatitis B vaccines, local and systemic adverse events were monitored daily for 14 days post-vaccination using a diary card. Local adverse events were only monitored at site/arm of Adacel vaccine administration. Unsolicited reactions (including immediate reactions, serious adverse events and events that elicited seeking medical attention) were collected at a clinic visit or via telephone interview for the duration of the trial, i.e., up to six months post-vaccination. In the concomitant vaccination study with Adacel vaccine and trivalent inactivated influenza vaccine, local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. All unsolicited reactions occurring through day 14 were collected. From day 14 to the end of the trial, i.e., up to 84 days, only events that elicited seeking medical attention were collected. In all the studies, participants were monitored for serious adverse events throughout the duration of the study. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

Serious Adverse Events in All Safety Studies Throughout the 6-month follow-up period in the principal safety study, serious adverse events were reported in 1.5% of Adacel vaccine recipients and 1.4% in Td vaccine recipients. Two serious adverse events in adults were neuroopathic events that occurred within 28 days of Adacel vaccine administration; one severe migraine with unilateral facial paralysis and one diagnosis of nerve compression in neck and left arm. Similar or lower rates of serious adverse events were reported in the other trials and there were no additional neuroopathic events reported.

Solicited Adverse Events in the Principal Safety Study Most selected solicited adverse events (erythema, swelling, pain and fever) that occurred during Days 0-14 following one dose of Adacel vaccine or Td vaccine were reported at a similar frequency. Few participants

R only

(<1%) sought medical attention for these reactions. Pain at the injection site was the most common adverse reaction occurring in 63 to 78% of all vaccinees. In addition, overall rates of pain were higher in adolescent recipients of Adacel vaccine compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the Adacel vaccine and Td vaccine groups. Among adults the rates of pain, after receipt of Adacel vaccine or Td vaccine, did not significantly differ. Fever of 38°C and higher was uncommon, although in the adolescent age group, it occurred significantly more frequently in Adacel vaccine recipients than Td vaccine recipients. (7) Among other solicited adverse events headache was the most frequent systemic reaction and was usually of mild to moderate intensity. In general, the rates of the events following Adacel vaccine were comparable with those observed with Td vaccine. Local and systemic solicited reactions occurred at similar rates in Adacel vaccine and Td vaccine recipients in the 3 day post-vaccination period. Most local reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days). The rates of unsolicited adverse events reported from days 14-28 post-vaccination were comparable between the two groups, as were the rates of unsolicited adverse events from day 28 through 6 months. There were no spontaneous reports of whole-arm swelling of the injected limb in this study, nor in the other three studies which contributed to the safety database for Adacel vaccine.

Adverse Events in the Concomitant Vaccine Studies

Local and Systemic Reactions when Given with Hepatitis B Vaccine The rates reported for fever and injection site pain (at the Adacel vaccine administration site) were similar when Adacel and Hep B vaccines were given concurrently or separately. However, the rates of injection site erythema (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the Adacel vaccine administration site were increased when co-administered. Swollen and/or sore joints were reported by 22.5% for concomitant vaccination and 17.9% for separate administration. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vaccination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups. (7)

Local and Systemic Reactions when Given with Trivalent Inactivated Influenza Vaccine The rates of fever and injection site erythema and swelling were similar for recipients of concurrent and separate administration of Adacel vaccine and TIV. However, pain at the Adacel vaccine injection site occurred at statistically higher rates following concurrent administration (66.6%) versus separate administration (60.8%). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% for separate administration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unsolicited adverse events were similar between the 2 study groups. (7)

Additional Studies An additional 1,806 adolescents received Adacel vaccine as part of the lot consistency study used to support Adacel vaccine licensure. This study was a randomized, double-blind, multi-center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of Adacel vaccine when given as a booster dose to adolescents 11-17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. Unsolicited adverse events and serious adverse events were collected for 28 days post-vaccination. Pain was the most frequently reported local adverse event occurring in approximately 80% of all participants. Headache was the most frequently reported systemic event occurring in approximately 44% of all participants. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days. (7) An additional 962 adolescents and adults received Adacel vaccine in three supportive Canadian studies used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following Adacel vaccine were similar to those reported in the four principal trials in the US with the exception of a higher rate (86%) of adults experiencing 'any' local injection site pain. The rate of severe pain (0.8%), however, was comparable to the rates reported in four principal trials conducted in the US. (7) There was one spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous reports among the 962 Adacel vaccine recipients in the supportive Canadian studies.

Postmarketing Reports The following adverse events have been spontaneously reported during the post-marketing use of Adacel vaccine in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on severity, frequency of reporting or the strength of causal association to Adacel vaccine. *General disorders and administration site conditions:* Large injection site reactions (>50 mm), extensive limb swelling from the injection site beyond one or both joints. Injection site bruising, sterile abscess. *Nervous system disorders:* Parosmia, hyposmia, Guillain-Barré syndrome, facial palsy, convulsion, syncope, myelitis. *Immune system disorders:* Anaphylactic reaction, hypersensitivity reaction (angioedema, edema, rash, hypotension). *Skin and subcutaneous tissue disorders:* Pruritus, urticaria. *Musculoskeletal and connective tissue disorders:* Myositis, muscle spasm. *Cardiac disorders:* Myocarditis.

Additional Adverse Events Additional adverse events, included in this section, have been reported in conjunction with receipt of vaccines containing diphtheria, tetanus toxoids and/or pertussis antigens. Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. Such reactions may be associated with high levels of circulating antitoxin in persons who have had overly frequent injections of tetanus toxoid. (8) (See **WARNINGS**.) Persistent nodules at the site of injection have been reported following the use of adsorbed products. (4) Certain neurological conditions have been reported in temporal association with some tetanus toxoid containing vaccines or tetanus and diphtheria toxoid containing vaccines. A review by the Institute of Medicine (IOM) concluded that the evidence favors acceptance of a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. Other neurological conditions that have been reported include: demyelinating diseases of the central nervous system, peripheral neuropathies, and cranial mononeuropathies. The IOM has concluded that the evidence is inadequate to accept or reject a causal relation between these conditions and vaccines containing tetanus and/or diphtheria toxoids.

Reporting of Adverse Events The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records of the manufacturer and lot number of the vaccine administered in the vaccine recipient's permanent medical record along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine. The Act further requires the health-care professional to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in the Vaccine Injury Table. These include anaphylaxis or anaphylactic shock within 7 days; brachial neuritis within 28 days; an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this Adacel vaccine package insert. (9-11) The US Department of Health and Human Services has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. Reporting of all adverse events occurring after vaccine administration is encouraged from vaccine recipients, parents/guardians and the health-care provider. Adverse events following immunization should be reported to VAERS. Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967 or visit the VAERS website at www.vaers.hhs.gov. (9-11) Health-care providers should also report these events to Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463 (1-800-VACCINE).

DOSAGE AND ADMINISTRATION Adacel vaccine should be administered as a single injection of one dose (0.5 mL) by the intramuscular route. Adacel vaccine should not be combined through reconstitution or mixed with any other vaccine. Just before use, shake the vial well until a uniform, white, cloudy suspension results. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, the vaccine should not be administered. When administering a dose from a rubber-stoppered vial, do not remove either the stopper or the metal seal holding it in place. The preferred site is into the deltoid muscle. The vaccine should not be injected into the gluteal area or areas where there is a major nerve trunk. Do NOT administer this product intravenously or subcutaneously. Five years should have elapsed since the recipient's last dose of tetanus toxoid, diphtheria toxoid and/or pertussis containing vaccine. There are no data to support repeat administration of Adacel vaccine. The use of Adacel vaccine as a primary series or to complete the primary series for tetanus, diphtheria, or pertussis has not been studied.

STORAGE Store 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.

REFERENCES 1. CDC. Preventing tetanus, diphtheria and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. MMWR 2006;55(RR-17):1-36. 2. CDC. Preventing tetanus, diphtheria and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. MMWR 2006;55(RR-3):1-35. 3. CDC. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(RR-15):1-48. 4. CDC. Update: vaccine side effects, adverse reactions, contraindications and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45(RR-12):1-35. 5. CDC. Diphtheria, tetanus and pertussis: recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(RR-10):1-28. 6. CDC. Update on adult immunization. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(RR-12):1-52. 7. Data on file at Sanofi Pasteur Limited. 8. Stratton KR, et al, editors. Adverse events associated with childhood vaccines: evidence bearing on causality. Washington: National Academy Press; 1994. p. 67-117. 9. CDC. Current trends - Vaccine Adverse Event Reporting System (VAERS) United States. MMWR 1990;39(41):730-3. 10. CDC. Current trends - national vaccine injury act: requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 1988;37(13):197-200. 11. FDA. New reporting requirements for vaccine adverse events. FDA Drug Bull 1988;18(2):16-8.

Product information as of January 2009.

Manufactured by:
Sanofi Pasteur Limited
Toronto Ontario Canada
MKT17204-2

sanofi pasteur

Printed in USA

Distributed by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA
RS-0109 USA
5751