

# New Hib Booster Vaccine Shores Up Supply

BY ELIZABETH MEHCATIE

The Food and Drug Administration has approved a new *Haemophilus influenzae* type b (Hib) vaccine for use as a booster dose in children aged 15 months through 4 years, providing another option for children whose boosters were deferred as a result of the nationwide Hib vaccine shortage that began almost 2 years ago.

The monovalent Hib vaccine is Hiberix (*Haemophilus b* conjugate vaccine [tetanus toxoid conjugate]), which is manufactured by GlaxoSmithKline (GSK). It was first marketed in Germany in 1996, and is now available in almost 100 countries, including the United States, according to the GSK Web site.

"This approval will provide an additional safe and effective vaccine to help ensure that there is an adequate Hib

vaccine supply during necessary catch-up vaccinations," Dr. Karen Midthun, acting director of the FDA's Center for Biologics Evaluation and Research, said in a statement.

Under its accelerated approval program, the FDA concluded that Hiberix was safe and effective as a booster dose in the United States, based on data from seven studies of more than 1,000 children that was conducted in Europe, Latin

America, and Canada. As a condition of the accelerated approval, GSK will conduct a postmarketing study of Hiberix in the United States, which will evaluate the safety and immunogenicity of Hiberix as a booster and primary vaccine, compared with a Hib vaccine that is already available in the United States, according to the statement.

The nationwide shortage of Hib vaccine dates back to December 2007, a result of a voluntary recall and subsequent suspension of Merck & Co.'s PedvaxHIB and COMVAX, two of the four Hib vaccines licensed in the United States for primary

## EPIPEN 2-PAK® EPIPEN Jr 2-PAK® (Epinephrine) Auto-Injectors 0.3/0.15mg

EpiPen® 0.3 mg EPINEPHRINE AUTO-INJECTOR  
EpiPen® Jr 0.15 mg EPINEPHRINE AUTO-INJECTOR

**BRIEF SUMMARY.** See package insert for full Prescribing Information.

**DO NOT REMOVE ACTIVATION CAP UNTIL READY FOR USE.**  
**THIS UNIT CONTAINS NO LATEX.**

**INDICATIONS AND USAGE:** EpiPen® and EpiPen® Jr Auto-Injectors are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquito), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. EpiPen® and EpiPen® Jr Auto-Injectors are intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Selection of the appropriate dosage strength is determined according to patient body weight (See DOSAGE AND ADMINISTRATION section of the full Prescribing Information).

Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, a thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

EpiPen® and EpiPen® Jr Auto-Injectors are intended for immediate self-administration as emergency supportive therapy only and are not a substitute for immediate medical care.

**CONTRAINDICATIONS:** There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

**WARNINGS:** EpiPen® and EpiPen® Jr Auto-Injectors should only be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK. Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis.

Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Treatment should be directed at vasodilation in addition to further treatment of anaphylaxis. (see ADVERSE REACTIONS). Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection.

**DO NOT INJECT INTRAVENOUSLY.** Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

Epinephrine should be administered with caution in patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, or anti-arrhythmics, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. It should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.

Epinephrine is light sensitive and should be stored in the carrier tube provided. Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) (See USP Controlled Room Temperature). Do not refrigerate. Before using, check to make sure the solution in the auto-injector is not discolored. Replace the auto-injector if the solution is discolored or contains a precipitate.

### PRECAUTIONS:

#### (1) General

EpiPen® and EpiPen® Jr Auto-Injectors are not intended as a substitute for immediate medical care. In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care. More than two sequential doses of epinephrine should only be administered under direct medical supervision.

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which epinephrine should be used. It must be clearly determined that the patient is at risk of future anaphylaxis, since the following risks may be associated with epinephrine administration (see DOSAGE AND ADMINISTRATION section of the full Prescribing Information).

Epinephrine should be used with caution in patients who have cardiac arrhythmias, coronary artery or organic heart disease, hypertension, or in patients who are on drugs that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, quinidine, or other anti-arrhythmics. In such patients, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Some patients may be at greater risk of developing adverse reactions after epinephrine administration. These include: hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, pediatric patients under 30 kg (66 lbs.) body weight using EpiPen® Auto-Injector, and pediatric patients under 15 kg (33 lbs.) body weight using EpiPen® Jr Auto-Injector.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen® or EpiPen® Jr Auto-Injector to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

#### (2) Information for Patients

Complete patient information, including dosage, direction for proper administration and precautions can be found inside each EpiPen®/EpiPen® Jr Auto-Injector carton.

Epinephrine may produce symptoms and signs that include an increase in heart rate, the sensation of a more forceful heartbeat, palpitations, sweating, nausea and vomiting, difficulty breathing, pallor, dizziness, weakness or shakiness, headache, apprehension, nervousness, or anxiety. These symptoms and signs usually subside rapidly, especially with rest, quiet and recumbency. Patients with hypertension or hyperthyroidism may develop more severe or persistent effects, and patients with coronary artery disease could experience angina. Patients with diabetes may develop increased blood glucose levels following epinephrine administration. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

In case of accidental injection, the patient should be advised to immediately go to the emergency room for treatment. Since the epinephrine in the EpiPen® Auto-Injector is a strong vasoconstrictor when injected into the digits, hands or feet, treatment should be directed at vasodilation if there is such an inadvertent administration to these areas. (see ADVERSE REACTIONS).

#### (3) Drug Interactions

Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levodopa, sodium, and certain antihistamines, notably chlorpheniramine, triprolenamine and diphenhydramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol. The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentolamine. Ergot alkaloids may also reverse the pressor effects of epinephrine.

#### (4) Carcinogenesis, Mutagenesis, Impairment of Fertility

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro* and to be an oxidative mutagen in a *W*2 bacterial reverse mutation assay. Epinephrine had a moderate degree of mutagenicity, and was positive in the DNA Repair test with *B. subtilis* (REC) assay, but was not mutagenic in the *Salmonella* bacterial reverse mutation assay. Studies of epinephrine after repeated exposure in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted. This should not prevent the use of epinephrine under the conditions noted under INDICATIONS AND USAGE.

#### (5) Use in Pregnancy

Pregnancy Category C: There is no study on the acute effect of epinephrine on pregnancy. Epinephrine has been shown to have developmental effects when administered subcutaneously in rabbits at a dose of 1.2 mg/kg daily for two to three days (approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m<sup>2</sup> basis), in mice at a subcutaneous dose of 1 mg/kg daily for 10 days (approximately 7 times the maximum daily subcutaneous or intramuscular dose on a mg/m<sup>2</sup> basis) and in hamsters at a subcutaneous dose of 0.5 mg/kg daily for 4 days (approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m<sup>2</sup> basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg daily for 10 days (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m<sup>2</sup> basis). Although, there are no adequate and well-controlled studies in pregnant women, epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

**ADVERSE REACTIONS:** Adverse reactions to epinephrine include transient, moderate anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or certain drugs [see PRECAUTIONS, Drug Interactions]. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in an acute life-threatening allergic reaction.

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area (see WARNINGS). Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pain, coldness and hypoaesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

**OVERDOSAGE:** Epinephrine is rapidly inactivated in the body and treatment following overdose with epinephrine is primarily supportive. If necessary, pressor effects may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking drugs. If prolonged hypotension follows such measure, it may be necessary to administer another pressor drug.

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients.

Overdosage may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Treatment consists of a rapidly acting alpha-adrenergic blocking drug and/or respiratory support.

Epinephrine overdose can also cause transient bradycardia followed by tachycardia and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (prebrilliant rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-blocking drug such as propranolol.

Overdosage sometimes results in extreme pallor and coldness of the skin, metabolic acidosis and kidney failure. Suitable corrective measures must be taken in such situations.

**HOW SUPPLIED:** EpiPen® Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) are available in individual cartons, NDC 49502-500-01, and as EpiPen 2-Pak®, NDC 49502-500-02, a pack that contains two EpiPen® Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) and one EpiPen® Auto-Injector trainer device.

EpiPen® Jr Auto-Injectors (epinephrine injection, USP, 1:2000, 0.3 mL) are available in individual cartons, NDC 49502-501-01, and as EpiPen Jr 2-Pak®, NDC 49502-501-02, a pack that contains two EpiPen® Jr Auto-Injectors (epinephrine injections, USP, 1:2000, 0.3 mL) and one EpiPen® Auto-Injector trainer device.

EpiPen 2-Pak® and EpiPen Jr 2-Pak® also includes an S-clip to clip two cases together.  
Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) (See USP Controlled Room Temperature).  
Contains no latex. Protect from light.

Rx only.

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03-500-03 (BR)

March 2009



'It is critical that providers ... return to including the [Hib] booster at this time.'

DR. SCHUCHAT

and booster doses. The shortage prompted the Centers for Disease Control and Prevention to recommend that the Hib booster be deferred for children who were not at high risk for infection, which was in effect from Dec. 18, 2007, through June 25, 2009. But after Sanofi-Aventis increased production of its Hib-containing vaccine doses in July 2009, the CDC recommended that the booster dose be reinstated with "limited catch-up" with the available monovalent and combination products.

Almost 3 weeks before the FDA's announcement, Dr. Anne Schuchat, director of the CDC's National Center for Immunization and Respiratory Diseases, stressed the "critical importance" of reinstating the booster dose of Hib vaccine in children aged 12-15 months, in a July 30 letter to health care providers. She said that the CDC was aware of some providers who were delaying administering the catch-up booster dose until supplies of a monovalent vaccine became available, but advised against this practice.

She noted that although there was enough Hib vaccine available to return to providing the three doses of primary vaccinations and the booster dose, the supply of the combination vaccine Pentacel (DTaP-IPV/Hib) was increasing, and the supply of the monovalent vaccine was "near stable." (At that time, Hiberix was not yet approved.) Therefore, "to reinstate the booster dose and maximize the number of children protected from Hib, most practices will need to incorporate DTaP-IPV/Hib, even if this is not their preference," she said.

"We believe that we are in the final stretch of the Hib vaccine shortage," Dr. Schuchat said in the July 30 letter. She said that CDC's Hib experts have not seen an increase in invasive Hib disease, but because of the potential for increased nasopharyngeal carriage of the Hib bacterium, "it is critical that providers continue to provide children with the full primary series and return to including the booster at this time."

