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TO: California Vaccines for Children (VFC) Program Providers

FROM: John Talarico, D.O., M.P.H., Chief
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SUBJECT: 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE [DIPHTHERIA CRM_{193} PROTEIN] (PCV13) IS NOW AVAILABLE FROM VFC TO REPLACE PCV7

SUMMARY

On February 24, 2010, the United States Food and Drug Administration (FDA) licensed a 13-valent pneumococcal conjugate vaccine (PCV13), Prevnar 13™, for the prevention of invasive disease and otitis media in children 6 weeks through 5 years (71 months) of age. PCV13 replaces the 7-valent pneumococcal conjugate vaccine (PCV7), Prevnar™. The federal Advisory Committee on Immunization Practices (ACIP) now recommends the routine use of PCV13 as a four-dose series at 2, 4, 6, and 12-15 months. PCV13 is now available from VFC for all VFC-eligible children 6 weeks through 5 years of age and for those with high risk conditions through age 18 years. The California Department of Public Health, Immunization Branch is following ACIP's recommendations for use of pneumococcal vaccines.

BACKGROUND

Streptococcus pneumoniae (pneumococcus) causes bacteremia, meningitis, pneumonia, empyema and other severe illnesses. It is also a cause of otitis media, sinusitis, and conjunctivitis. Prior to the licensure of PCV7 in 2000, *S. pneumoniae* was the most common cause of invasive bacterial disease in children older than one month of age. PCV7 protects against pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Since the introduction of PCV7, invasive pneumococcal disease among children younger than age five years in the U.S. has decreased by 76%. Invasive pneumococcal disease has also decreased in adults, presumably through decreased transmission and carriage after immunization of children with PCV7.

However, infections caused by additional pneumococcal serotypes have subsequently increased. Pneumococcal serotype 19A is currently the most common cause of invasive bacterial disease in children. PCV13 also protects against serotypes 1, 3, 5, 6A, 7F, and 19A, which in one US study have been associated with 64% of recent cases of invasive pneumococcal disease of known serotype in children younger than 5 years.

Pneumococcal infections are most common in infants, young children, elderly persons, and black, Alaska Native, and some American Indian populations. In addition, those with congenital or acquired humoral immunodeficiency, human immunodeficiency virus (HIV) infection, absent or deficient splenic function (e.g., sickle cell disease, functional or anatomic asplenia), other immunocompromising conditions, and certain chronic health conditions are at higher risk of pneumococcal infection or more severe disease. Children with cochlear implants have high rates of pneumococcal meningitis.

COMPOSITION

PCV13 is a sterile suspension of saccharides of the capsular antigens of the 13 pneumococcal serotypes individually conjugated to CRM_{197} protein, a nontoxic variant of diphtheria toxin isolated from cultures of *C. diphtheriae* strain C7 (β197) grown in casamino acids and yeast extract-based medium. The polysaccharides of the capsular antigens of the 13 serotypes included in the vaccine are purified and chemically activated to make saccharides, which are then conjugated to the protein carrier CRM_{197} to form the glycoconjugates. The individual glycoconjugates are purified and compounded to formulate the vaccine.

Each 0.5mL dose of PCV13 is formulated to contain approximately 2.2 mcg of each of the *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides, 4.4 mcg of 6B saccharides, and 34 mcg CRM_{197} carrier protein. The vaccine also contains 125 mcg aluminum as aluminum phosphate adjuvant.

The tip cap and rubber plunger of the pre-filled syringe do not contain latex. The vaccine contains no thimerosal preservative.

Immunogenicity was compared between PCV13 and PCV7. In recipients of PCV13 pneumococcal anti-capsular polysaccharide IgG antibody concentrations were non-inferior for 10 of 13 serotypes after 3 doses (exceptions, serotypes 6B, 9V, and 3) and 12 of 13 serotypes after 4 doses (exception, serotype 3) Opsonophagocytosis assay (OPA) antibodies were comparable between recipients of PCV13 and PCV7 for all serotypes. See product insert for more details.

RECOMMENDATIONS FOR PCV13 VACCINE USE IN THE VFC PROGRAM

Children Eligible for VFC Supplies of PCV13
Children eligible for PCV 13 under VFC include ages

- 6 weeks through 59 months regardless of underlying conditions
- 60 through 71 months of age with conditions that increase their risk of pneumococcal disease or its complications (see below)
- 6 through 18 years with sickle cell disease, HIV infection or other immunocompromising conditions, cochlear implants, or CSF leaks.

ACIP and CDPH Recommendations for PCV13

ACIP and CDPH recommend PCV13 for

- all children 2 through 59 months of age and
- children 60 through 71 months of age with certain underlying medical conditions that increase their risk of pneumococcal disease or its complications, including:
    - Chronic heart disease, particularly cyanotic congenital heart disease and cardiac failure
    - Chronic lung disease, including asthma if on prolonged high-dose oral corticosteroids
    - Diabetes mellitus
    - Cerebrospinal fluid leaks
    - Cochlear implant
    - Children with functional or anatomic asplenia
        - Sickle cell disease and other hemoglobinopathies
        - Congenital or acquired asplenia, or splenic dysfunction
    - Children with immunocompromising conditions
        - HIV infection
        - Chronic renal failure and nephrotic syndrome
        - Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation
        - Congenital immunodeficiency, including B- or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency, and phagocytic disorders (excluding chronic granulomatous disease).

1. Routine schedule for children who have not previously received PCV7 or PCV13
The recommended immunization schedules for children 2 through 59 months of age who have not received any prior PCV7 or PCV13 doses are unchanged from those previously published for PCV7, except that PCV13 now replaces PCV7 for all doses.

- **Infants 2 through 6 months of age**
  PCV13 is recommended as a 4-dose series at 2, 4, 6, and 12--15 months, similar to PCV7. Infants receiving their first dose when younger than 6 months should receive 3 doses of PCV13 at intervals of approximately 8 weeks (the minimum interval is 4 weeks). The minimum age for administration of first dose is 6 weeks. The fourth dose is recommended at age 12--15 months and should be given at least 8 weeks after the third dose (Table 1).

- **Unvaccinated children at least 7 months of age**
  For previously unvaccinated children 7 months of age and older, please see Table 1.

2. Children incompletely vaccinated with PCV7 or PCV13

- **Children <24 months of age**
  who have received one or more doses of PCV7 should complete the immunization series with PCV13 (Table 2).

- **Children at least 24 months of age**

For all healthy children 24 through 59 months of age with an incomplete PCV7 or PCV13 schedule, a single dose of PCV13 is recommended, similar to prior recommendations for PCV 7.

For children 24 through 71 months of age with underlying medical conditions who have received:

- 0-2 doses of PCV7 or PCV13: 2 doses of PCV13 are recommended.
- 3 doses of PCV7 or PCV13: 1 dose of PCV13 is recommended

The minimum interval between doses is 8 weeks.

3. Children completely vaccinated with PCV7 - give 1 more dose of PCV13
For all healthy children 14 through 59 months of age who are completely vaccinated with PCV7, a single supplemental dose of PCV13 is recommended (Table 2).

For all children with underlying medical conditions who are 14 through 71 months of age and completely vaccinated with PCV7, a single supplemental dose of PCV13 is recommended (Table 2). This includes children who have previously received the 23-valent pneumococcal polysaccharide vaccine (PPSV23).

The minimum interval between doses, including doses of PPSV23, is 8 weeks

For children 6 through 18 years of age with sickle cell disease, HIV-infection or other immunocompromising condition, cochlear implant or cerebrospinal fluid leaks, a single supplemental dose of PCV13 may be administered regardless of prior receipt of PCV7 or PPSV23. Routine use of PCV13 is not recommended for healthy children ≥ 5 years.

Use of PPSV23 among children 2 through 18 years of age who are at increased risk for invasive pneumococcal disease
Children with underlying medical conditions should also receive PPSV23 at age 2 years or as soon as possible after the diagnosis of chronic illness is made at older ages. Doses of PCV13 should be completed before PPSV23 is given. The minimum interval is at least 8 weeks after the last dose of PCV13. However, children who have previously received PPSV23 should also receive the recommended PCV13 doses.

A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23 for children who have sickle cell disease, or functional or anatomic asplenia, HIV-infection, or other immunocompromising condition. No more than two PPSV23 doses are recommended.

Transition from PCV7 to PCV13 within your Office:
Your office will be replacing PCV7 with PCV13. Please make sure to review the updated ACIP recommendations and to train your entire office staff regarding the implications of this transition for your practice. This transition will affect your vaccine ordering, billing, and documentation.

Please make sure to understand the implications of both catch-up vaccination and vaccination of high-risk patients when placing your orders.

Until doses of PCV13 are received at your practice, PCV7 should be administered to those children and infants who are due for their next PCV dose. Once doses of PCV13 arrive, children should complete their series with PCV13 at their next routine visit (rather than through mass recall) according to the current ACIP recommendations provided in this letter. After receipt of PCV13, any remaining unused doses of PCV7 should be immediately returned to VFC's national distributor by April 30, 2010 (see details under Return of Unused Inventory).

Table 1: Recommended Routine Vaccination Schedule for PCV13 Among Infant and Children who have not Received a Previous dose of PCV7 or PCV13, by Age at First Dose

Age at first dose (months)	Primary PCV13 Series*	PCV13 booster dose†
2-6	3 doses	1 dose at age 12-15 months
7-11	2 doses	1 dose at age 12-15 months
12-23	2 doses	-
24-59 (Healthy children)	1 dose	-
24-71 (Children with certain chronic diseases or immunocompromising conditions)	2 doses	-

*For children vaccinated at age <12 months, the minimum interval between doses is 4 weeks; otherwise, minimum interval between doses of 8 weeks.
†Given at least 8 weeks after the previous dose.

Table 2: Recommended Transition Schedule from PCV7 to PCV13, according to previous PCV7 doses received

Infant Series			Booster Dose	Supplemental PCV13 Dose
2 Months	**4 Months**	**6 Months**	**≥ 12 Months**	**14-59 Months**
PCV7	PCV13	PCV13	PCV13	-
PCV7	PCV7	PCV13	PCV13	-
PCV7	PCV7	PCV7	PCV13	-
PCV7	PCV7	PCV7	PCV7	PCV13‡

‡For children with underlying medical conditions, a single supplemental PCV13 dose is recommended through age 71 months. A supplemental PCV13 dose may also be given for those 6 through 18 years of age for persons with sickle cell disease, HIV-infection or other immunocompromising condition, cochlear implant or cerebrospinal fluid leak.

Tables adapted from: MMWR, 2020. 59(9): 250.

ADMINISTRATION OF PCV13
The vaccine syringe should be inspected carefully prior to administration; the vaccine should not be administered if the syringe is cracked or if particulate matter or discoloration is noted. Shake the syringe vigorously immediately prior to use to resuspend vaccine. Vaccine should be a homogenous, white suspension after shaking. Do not use vaccine if the product cannot be resuspended.

The 0.5 mL vaccine dose should be administered intramuscularly in the anterolateral aspect of the thigh of infants and the deltoid muscle of toddlers and young children.

Administration of PCV13 with other vaccines
PCV13 vaccine may be given at the same visit when other age appropriate vaccines are provided. Vaccines should be given in separate syringes and different injection sites (at least one inch apart). Do not mix Prevnar 13™ with other vaccines/products in the same syringe.

HOW SUPPLIED FOR CALIFORNIA VFC PROGRAM PROVIDERS
PCV13 is supplied as a package of 10 pre-filled syringes (NDC 0005-1971-02).

Storage
- PCV13 should be refrigerated at 35 - 46 degrees F (2 - 8 degrees C).
- Do not freeze.

POTENTIAL VACCINE REACTIONS
The incidence and severity of solicited local and systemic reactions to PCV13 is comparable with those to PCV7. The most common reports within 7 days after administration of PCV13 were injection-site reactions, fever, decreased appetite, irritability, and increased or decreased sleep.

Providers should report suspected reactions to PCV13 or other vaccines to the Vaccine Adverse Events Reporting System (VAERS) at 800-822-7967 (toll-free) or http://vaers.hhs.gov.

CONTRAINDICATIONS
- History of severe allergic reaction (e.g., anaphylaxis) to any component of PCV13, PCV7 or any diphtheria toxoid-containing vaccine (please see product insert for more details).

PRECAUTIONS
- Pneumococcal conjugate vaccines can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infections, with or without fever).
- Vaccination of people with moderate or severe acute illnesses should be deferred until after the illness improves.

ORDERING AND BILLING

How to Order
VFC Providers will be automatically transitioned from the 7-valent pneumococcal conjugate vaccine to the 13-valent pneumococcal conjugate vaccine. All PCV vaccine requests received as of March 18, 2010, are automatically being fulfilled with the new 13-valent pneumococcal conjugate vaccine. VFC Providers should review the provisional ACIP Recommendations for Use of Pneumococcal Conjugate Vaccines with their staff to transition from PCV7 to PCV13.

There will be no changes to the current version of the VFC Order Form (CDPH 8501 (03/10). Routine orders for the 13-valent pneumococcal conjugate vaccine may be submitted using the current form. Remember to complete all the boxes in the four columns of the order form and accurately account for all VFC vaccine doses received since with your previous order, plus doses reported on-hand in your previous order. Maintain a copy of your order forms for your office files.

Supplemental Orders

In an effort to reduce existing PCV7 inventories, VFC actively reduced provider requests for this vaccine during the weeks prior to the product transition. If your clinic received a reduced order for PCV7, you may re-submit a supplemental order for PCV13 to last until your next regular order.

Return of Unused Inventory of PCV7

Providers with existing supplies of PCV7 should return unused doses to VFC's national vaccine distributors as soon as requested doses of PCV13 arrive. **Doses must be returned by April 30th, 2010**. The new federal contract price for each 10-dose box of this product is $917.50. Please ensure your clinic returns any unused doses for significant cost savings to the program.

Unused doses should be returned following the same return procedure for non-viable VFC vaccine returns. A VFC Return/Transfer Form must be included in the vaccine shipment and also faxed to the VFC Program. You may obtain a copy at www.eziz.org. A return label may be requested by contacting the VFC Program's Customer Service Center.

Billing Information for VFC PCV13 Vaccine

Child Health and Disability Prevention Program (CHDP): The CHDP administration fee is $9.00 using CHDP code 88 for up to 5 doses of the 13-valent pneumococcal conjugate vaccine supplied by VFC administered to children through the age of 18 years enrolled in the CHDP Program.

However, providers should wait until notified by CHDP to submit claims for the 13-valent pneumococcal conjugate vaccine. CHDP Provider Information Notices can be found at http://www.dhcs.ca.gov/formsandpubs/publications/Pages/CMSLetters.aspx.

Medi-Cal Fee-For-Service (FFS):

Providers should wait until information is published in the Medi-Cal provider bulletin to submit claims as the specific codes and their implementation date are not final until published in the Medi-Cal provider bulletin (http://files.medi-cal.ca.gov/pubsdoco/Bulletins_menu.asp). Services are not considered benefits of the Medi-Cal Program until published in the Provider Bulletin. Providers should check the Medi-Cal provider manual for final codes and implementation date(s). The provider manual can be downloaded at: http://files.medi-cal.ca.gov/pubsdoco/publications/masters-mtp/part2/vaccine_m00o03o04o11.doc.

Other codes for the use of pneumococcal conjugate vaccine that is not supplied by VFC:

- The CPT code for 13-valent pneumococcal conjugate vaccine is **90670**.
- The ICD-9-CM code for the need for prophylactic vaccination against pneumococcus is **V03.82**.

DOCUMENTATION

- PCV13 Product Insert:contains additional vaccine information:
- Vaccine Information Statement (VIS): http://www.cdc.gov/vaccines/pubs/vis/default.htm.
- ACIP recommendations: http://www.cdc.gov/vaccines/pubs/ACIP-list.htm
- Invasive Pneumococcal Disease in Young Children Before Licensure of 13-Valent Pneumococcal Conjugate Vaccine—United States, 2007. http://www.cdc.gov/mmwr/PDF/wk/mm5909.pdf
- Preventing Pneumococcal Disease Among Infants and Young Children. MMWR 2000; 49(RR-9). http://www.cdc.gov/mmwr/PDF/rr/rr4909.pdf
- CDC Provider and Parent Q & A: will be available at www.cdc.gov/vaccines .
- AAP recommendations (members-only): http://www.cispimmunize.org/
- VFC resolution No. 02/10-1: The VFC resolution on pneumococcal conjugate vaccines can be found at: http://www.cdc.gov/vaccines/programs/vfc/acip-vfc-resolutions.htm.
- Vaccine Injury Compensation Program (VICP) covers PCV13 vaccine. Information on the federal VICP and pneumococcal vaccines will be found at: http://www.hrsa.gov/vaccinecompensation/.

Enclosures: Order Form (03/10)

cc: CDPH Immunization Branch Field Representatives
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