Patient Information

Aptivus® (ap' · ti · vəs) (tipranavir) **Capsules, 250 mg**	Boehringer Ingelheim

ALERT: Find out about medicines that should not be taken with Aptivus. Please also read the section "WHO SHOULD NOT TAKE APTIVUS".

Read the Patient Information that comes with APTIVUS before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. You should stay under a doctor's care while taking APTIVUS.

What is the most important information I should know about APTIVUS?

Patients taking APTIVUS, together with 200 mg NORVIR® (ritonavir), may develop severe liver disease that can cause death. If you develop any of the following symptoms of liver problems, you should stop taking APTIVUS/ritonavir treatment and call your doctor right away: tiredness, general ill feeling or "flu-like" symptoms, loss of appetite, nausea (feeling sick to your stomach), yellowing of your skin or whites of your eyes, dark (tea-colored) urine, pale stools (bowel movements), or pain, ache, or sensitivity on your right side below your ribs. If you have chronic Hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems.

What is APTIVUS?

APTIVUS is a medicine called a "protease inhibitor" that is used to treat adults with Human Immunodeficiency Virus (HIV). APTIVUS blocks HIV protease, an enzyme which is needed for HIV to make more virus. When used with other anti-HIV medicines, APTIVUS may reduce the amount of HIV in your blood and increase the number of CD4+ cells. Reducing the amount of HIV in the blood may keep your immune system healthy, so it can help fight infection.

APTIVUS is always taken with NORVIR® (ritonavir) and at the same time as NORVIR When you take APTIVUS with NORVIR, you must always use at least 2 other anti-HIV medicines.

Does APTIVUS cure HIV or AIDS?

APTIVUS does not cure HIV infection or AIDS. The long-term effects of APTIVUS are not known at this time. People taking APTIVUS may still get infections or other conditions common in people with HIV (opportunistic infections). It is very important that you stay under the care of your doctor during treatment with APTIVUS.

Does APTIVUS lower the chance of passing HIV to other people?

APTIVUS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. Continue to practice safer sex. Use a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Never use or share dirty needles.

Ask your doctor if you have any questions about safer sex or how to prevent passing HIV to other people.

Who should not take APTIVUS?

Do not take APTIVUS if you:

- are allergic to tipranavir or any of the other ingredients in APTIVUS. See the end of this leaflet for a list of major ingredients.
- are allergic to ritonavir (NORVIR®)
- have moderate to severe liver problems
- take any of the following types of medicines because **you could have serious side effects:**
    - Migraine headache medicines called "ergot alkaloids". If you take migraine headache medicines, ask you doctor or pharmacist if any of them are "ergot alkaloids".
    - Halcion® (triazolam)
    - Hismanal® (astemizole)
    - Orap® (pimozide)
    - Propulsid® (cisapride)
    - Seldane® (terfenadine)
    - Versed® (midazolam)
    - Pacenone® (amiodarone)
    - Vascor® (bepridil)
    - Tambocor® (flecainide)
    - Rythmol® (propafenone)
    - Quinaglute dura® (quinidine)

What should I tell my doctor before I take APTIVUS?

Tell your doctor about all of your medical conditions, including if you:

- **have liver problems** or are infected with Hepatitis B or Hepatitis C. These patients may have worsening of their liver disease.
- **are allergic to sulfa medicines.**
- **have hemophilia.** APTIVUS may cause increased bleeding.
- **have diabetes.** APTIVUS may worsen your diabetes or high blood sugar levels.

- **are pregnant or planning to become pregnant.** It is not known if APTIVUS can harm your unborn baby. You and your doctor will need to decide if APTIVUS is right for you. If you take APTIVUS while you are pregnant, talk to your doctor about how you can be in the Antiretroviral Pregnancy Registry.

- **are breast-feeding.** Do not breast-feed if you are taking APTIVUS. You should not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. Talk with your doctor about the best way to feed your baby.

- **are using estrogens for birth control or hormone replacement.** Women who use estrogens for birth control or hormone replacement have an increased chance of developing a skin rash while taking APTIVUS. If a rash occurs, it is usually mild to moderate, but you should talk to your doctor as you may need to temporarily stop taking either APTIVUS or the other medicine that contains estrogen or female hormones.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. **APTIVUS and many other medicines can interact. Sometimes serious side effects will happen if APTIVUS is taken with certain other medicines (see "Who should not take APTIVUS?").**

- Some medicines cannot be taken at all with APTIVUS
- Some medicines will require a change in dosage if taken with APTIVUS
- Some medicines will require close monitoring if taken with APTIVUS.

Women taking birth control pills need to use another birth control method. APTIVUS makes birth control pills work less well.

Know all the medicines you take and keep a list of them with you. Show this list to all your doctors and pharmacists anytime you get a new medicine you take. They will tell you if you can take these other medicines with APTIVUS. **Do not start any new medicines while you are taking APTIVUS without first talking with your doctor or pharmacist.** You can ask your doctor or pharmacist for a list of medicines that can interact with APTIVUS.

How should I take APTIVUS?

- Take APTIVUS exactly as your doctor has prescribed. You should check with your doctor or pharmacist if you are not sure. **You must take APTIVUS at the same time as NORVIR® (ritonavir).** The usual dose is 500 mg (two 250 mg capsules) of APTIVUS, together with 200 mg (two 100 mg capsules or 2.5 mL of solution) of NORVIR, twice per day. APTIVUS with NORVIR must be used together with other anti-HIV medicines.

APTIVUS comes in a capsule form and you should **swallow APTIVUS capsules whole. Do not chew the capsules.**

- Always take APTIVUS with food.
- Do not change your dose or stop taking APTIVUS without first talking with your doctor.
- If you take too much APTIVUS, call your doctor or poison control center right away.
- If you forget to take APTIVUS, take the next dose of APTIVUS, together with NORVIR® (ritonavir), as soon as possible. Do not take a double dose to make up for a missed dose.

- It is very important to take all your anti-HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop working to fight HIV (drug resistance).
- When your APTIVUS supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short period of time. The HIV virus may develop resistance to APTIVUS and become harder to treat. You should NEVER stop taking APTIVUS or your other HIV medicines without talking with your doctor.

What are the possible side effects of APTIVUS?

APTIVUS may cause serious side effects, including:

- **liver problems, including liver failure and death.** Your doctor should do blood tests to monitor your liver function during treatment with APTIVUS. Patients with liver diseases such as Hepatitis B and Hepatitis C may have worsening of their liver disease with APTIVUS and should have more frequent monitoring blood tests.

- **rash.** Mild to moderate rash, including flat or raised rashes or sensitivity to the sun, have been reported in approximately 10% of subjects receiving APTIVUS. Some patients who developed rash also had joint pain or stiffness, throat tightness, or generalized itching.

- **increased bleeding in patients with hemophilia.** This can happen in patients taking APTIVUS or other protease inhibitor medicines.

- **diabetes and high blood sugar (hyperglycemia).** This can happen in patients taking APTIVUS or other protease inhibitor medicines. Some patients have diabetes before starting treatment with APTIVUS which gets worse. Some patients get diabetes during treatment with APTIVUS. Some patients will need changes in their diabetes medicine. Some patients will need new diabetes medicine.

- **increased blood fat (lipid) levels.** Your doctor should do blood tests to monitor your blood fat (triglycerides and cholesterol) during treatment with APTIVUS. Some patients taking APTIVUS have large increases in triglycerides and cholesterol. The long-term chance of having a heart attack or stroke due to increases in blood fats caused by APTIVUS is not known at this time.

- **changes in body fat.** These changes have happened in patients taking APTIVUS. and other anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects include diarrhea, nausea, vomiting, stomach pain, tiredness and headache. Women taking birth control pills may get a skin rash.

It may be hard to tell the difference between side effects caused by APTIVUS, by the other medicines you are also taking, or by the complications of HIV infection. For this reason it is very important that

you tell your doctor about any changes in your health. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

The list of side effects is **not** complete. Ask your doctor or pharmacist for more information.

How should I store APTIVUS?

- Store APTIVUS capsules in a refrigerator at approximately **36°F to 46°F (2°C to 8°C).** Once the bottle is opened, the contents must be used within 60 days. Patients may take the bottle with them for use away from home so long as the bottle remains at a temperature of approximately **59°F to 86°F (15°C to 30°C).** You can write the date of opening the bottle on the label. Do not use after the expiration date written on the bottle.

- **Keep APTIVUS and all medicines out of the reach of children.**

General advice about APTIVUS

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use APTIVUS for a condition for which it was not prescribed. Do not give APTIVUS to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about APTIVUS. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about APTIVUS that is written for health professionals.

For additional information, you may also call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906. You may also request information through the company website at http://us.boehringer-ingelheim.com.

What are the ingredients in APTIVUS?

Active Ingredient: tipranavir

Major Inactive Ingredients: dehydrated alcohol, polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.

Rx only

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

APTIVUS is a registered trademark used under license from Boehringer Ingelheim International GmbH

APTIVUS Capsules are covered by U.S. Patents 5,852,195, 6,147,095, 6,169,181 and 6,231,887

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Poliovirus Vaccine Inactivated

IPOL®

IPV

℞ only

DESCRIPTION

IPOL®, Poliovirus Vaccine Inactivated, produced by Sanofi Pasteur SA, is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). IPOL vaccine is a highly purified, inactivated poliovirus vaccine with enhanced potency. Each of the three strains of poliovirus is individually grown in vero cells, a continuous line of monkey kidney cells cultivated on microcarriers.[1,2] The cells are grown in Eagle MEM modified medium, supplemented with newborn calf serum tested for adventitious agents prior to use, originated from countries free of bovine spongiform encephalopathy. For viral growth the culture medium is replaced by M-199, without calf serum. This culture technique and improvements in purification, concentration and standardization of poliovirus antigen produce a more potent and consistent immunogenic vaccine than the inactivated poliovirus vaccine (IPV) available in the US prior to 1988.[3,4]

After clarification and filtration, viral suspensions are concentrated by ultrafiltration, and purified by three liquid chromatography steps; one column of anion exchanger, one column of gel filtration and again one column of anion exchanger. After re-equilibration of the purified viral suspension, with Medium M-199 and adjustment of the antigen titer, the monovalent viral suspensions are inactivated at +37°C for at least 12 days with 1:4000 formalin.

Each dose (0.5 mL) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus. For each lot of IPOL vaccine, D-antigen content is determined *in vitro* using the D-antigen ELISA assay and immunogenicity is determined by *in vivo* testing in animals. IPOL vaccine is produced from vaccine concentrates diluted with M-199 medium. Also present are 0.5% of 2-phenoxyethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. Neomycin, streptomycin and polymyxin B are used in vaccine production, and although purification procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin and 25 ng polymyxin B per dose may still be present. The residual calf serum protein is less than 1 ppm in the final vaccine.

The vaccine is clear and colorless and should be administered intramuscularly or subcutaneously.

CLINICAL PHARMACOLOGY

Poliomyelitis is caused by poliovirus Types 1, 2, or 3. It is primarily spread by the fecal-oral route of transmission but may also be spread by the pharyngeal route.

Approximately 90% to 95% of poliovirus infections are asymptomatic. Nonspecific illness with low-grade fever and sore throat (minor illness) occurs in 4% to 8% of infections. Aseptic meningitis occurs in 1% to 5% of patients a few days after the minor illness has resolved. Rapid onset of asymmetric acute flaccid paralysis occurs in 0.1% to 2% of infections, and residual paralytic disease involving motor neurons (paralytic poliomyelitis) occurs in approximately 1 per 1,000 infections.[5]

Prior to the introduction of inactivated poliovirus vaccines in 1955, large outbreaks of poliomyelitis occurred each year in the United States (US). The annual incidence of paralytic disease of 11.4 cases/100,000 population declined to 0.5 cases by the time oral poliovirus vaccine (OPV) was introduced in 1961. Incidence continued to decline thereafter to a rate of 0.002 to 0.005 cases per 100,000 population. Of the 127 cases of paralytic poliomyelitis reported in the US between 1980 and 1994, six were imported cases (caused by wild polioviruses), two were "indeterminate" cases, and 119 were vaccine associated paralytic poliomyelitis (VAPP) cases associated with the use of live, attenuated oral poliovirus vaccine (OPV).[6] An all IPV schedule was adopted in 1999, to eliminate VAPP cases.[7]

Poliovirus Vaccine Inactivated induces the production of neutralizing antibodies against each type of virus which are related to protective efficacy. Antibody response in most children were induced after receiving fewer doses[8] of IPV vaccine than the vaccine available in the United States prior to 1988.

Studies in developed[8] and developing[9,10] countries with a similar enhanced IPV manufactured by the same process as IPOL vaccine in primary monkey kidney cells have shown a direct relationship exists between the antigenic content of the vaccine, the frequency of seroconversion, and resulting antibody titer. Approval in the US was based upon demonstration of immunogenicity and safety in US children.[11]

In the US, 219 infants received three doses of a similar enhanced IPV at two, four and eighteen months of age manufactured by the same process as IPOL vaccine except the cell substrate for IPV was using primary monkey kidney cells. Seroconversion to all three types of poliovirus was demonstrated in 99% of these infants after two doses of vaccine given at 2 and 4 months of age. Following the third dose of vaccine at 18 months of age, neutralizing antibodies were present at a level of ≥1:10 in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses.[3]

IPOL vaccine was administered to more than 700 infants between 2 to 18 months of age during three clinical studies conducted in the US using IPV only schedules and sequential IPV-OPV schedules.[12,13] Seroprevalence rates for detectable serum neutralizing antibody (DA) at a ≥1:4 dilution were 95% to 100% (Type 1); 97% to 100% (Type 2) and 96% to 100% (Type 3) after two doses of IPOL vaccine depending on studies.

TABLE 1 US STUDIES WITH IPOL VACCINE ADMINISTERED USING IPV ONLY OR SEQUENTIAL IPV-OPV SCHEDULES

Age (months) for				Post Dose 2				Post Dose 3				Pre Booster				Post Booster			
2	4	6	12 to 18		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3
Dose 1	Dose 2	Dose 3	Booster	N*	%DA**	%DA	%DA	N*	%DA	%DA	%DA	N*	%DA	%DA	%DA	N*	%DA	%DA	%DA
STUDY 1[11¶]																			
I(s)	I(s)	NA†	I(s)	56	97	100	97		–	–	–	53	91	97	93	53	97	100	100
O	O	NA	O	22	100	100	100		–	–	–	22	78	91	78	20	100	100	100
I(s)	O	NA	O	17	95	100	95		–	–	–	17	95	100	95	17	100	100	100
I(s)	I(s)	NA	O	17	100	100	100		–	–	–	16	100	100	94	16	100	100	100
STUDY 2[10§]																			
I(c)	I(c)	NA	I(s)	94	98	97	96		–	–	–	100	92	95	88	97	100	100	100
I(s)	I(s)	NA	I(s)	68	99	100	99		–	–	–	72	100	100	94	75	100	100	100
I(c)	I(c)	NA	O	75	95	99	96		–	–	–	77	86	97	82	78	100	100	97
I(s)	I(s)	NA	O	101	99	99	95		–	–	–	103	99	97	89	107	100	100	100
STUDY 3[10§]																			
I(c)	I(c)	I(c)	O	91	98	99	100	91	100	100	100	41	100	100	100	40	100	100	100
I(c)	I(c)	O	O	96	100	98	99	94	100	100	99	47	100	100	100	45	100	100	100
I(c)	I(c)	I(c) + O	O	91	96	97	100	85	100	100	100	47	100	100	100	46	100	100	100

* N = Number of children from whom serum was available
** Detectable antibody (neutralizing titer ≥1:4)
† NA – No poliovirus vaccine administered
¶ IPOL vaccine given subcutaneously
§ IPOL vaccine given intramuscularly
I IPOL vaccine given either separately in association with DTP in two sites (s) or combined (c) with DTP in a dual chambered syringe
O OPV

In one study,[13] the persistence of DA in infants receiving two doses of IPOL vaccine at 2 and 4 months of age was 91% to 100% (Type 1), 97% to 100% (Type 2), and 93% to 94% (Type 3) at twelve months of age. In another study,[12] 86% to 100% (Type 1), 95% to 100% (Type 2), and 82% to 94% (Type 3) of infants still had DA at 18 months of age.

In trials and field studies conducted outside the US, IPOL vaccine, or a combination vaccine containing IPOL vaccine and DTP, was administered to more than 3,000 infants between 2 to 18 months of age using IPV only schedules and immunogenicity data are available from 1,485 infants. After two doses of vaccine given during the first year of life, seroprevalence rates for detectable serum neutralizing antibody (neutralizing titer ≥1:4) were 88% to 100% (Type 1); 84% to 100% (Type 2) and 94% to 100% (Type 3) of infants, depending on studies. When three doses were given during the first year of life, post-dose 3 DA ranged between 93% to 100% (Type 1); 89% to 100% (Type 2) and 97% to 100% (Type 3) and reached 100% for Types 1, 2, and 3 after the fourth dose given during the second year of life (12 to 18 months of age).[14]

In infants immunized with three doses of an unlicensed combination vaccine containing IPOL vaccine and DTP given during the first year of life, and a fourth dose given during the second year of life, the persistence of detectable neutralizing antibodies was 96%, 96% and 97% against poliovirus Types 1, 2, and 3, respectively, at six years of age. DA reached 100% for all types after a booster dose of IPOL vaccine combined with DTP vaccine.[11] A survey of Swedish children and young adults given a Swedish IPV only schedule demonstrated persistence of detectable serum neutralizing antibody for at least 10 years to all three types of poliovirus.[15]

IPV is able to induce secretory antibody (IgA) produced in the pharynx and gut and reduces pharyngeal excretion of poliovirus Type 1 from 75% in children with neutralizing antibodies at levels less than 1:8 to 25% in children with neutralizing antibodies at levels more than 1:64.[4,14,16-22] There is also evidence of induction of herd immunity with IPV,[15,23-26] and that this herd immunity is sufficiently maintained in a population vaccinated only with IPV.[26]

VAPP has not been reported in association with administration of IPOL vaccine.[27] It is expected that an IPV only schedule will eliminate the risk of VAPP in both recipients and contacts compared to a schedule that included OPV.[7]

INDICATIONS AND USAGE

IPOL vaccine is indicated for active immunization of infants (as young as 6 weeks of age), children and adults for the prevention of poliomyelitis caused by poliovirus Types 1, 2, and 3.[28]

INFANTS, CHILDREN AND ADOLESCENTS

General Recommendations

It is recommended that all infants (as young as 6 weeks of age), unimmunized children and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.[29] Following the eradication of poliomyelitis caused by wild poliovirus from the Western Hemisphere (including North and South America).[30] An IPV-only schedule was recommended to eliminate VAPP.[7]

All children should receive four doses of IPV at ages 2, 4, 6 to 18 months and 4 to 6 years. OPV is no longer available in the US and is not recommended for routine immunization.[7] OPV is only recommended for special circumstances including the control of outbreaks.

Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with IPOL vaccine.

Children Incompletely Immunized

Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of four doses is reached (see **DOSAGE AND ADMINISTRATION** section).

ADULTS

General Recommendations

Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the US is not recommended. Unimmunized adults who are potentially exposed to wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the **DOSAGE AND ADMINISTRATION** section.[28]

Persons with previous wild poliovirus disease who are incompletely immunized or unimmunized should be given additional doses of IPOL vaccine if they fall into one or more categories listed previously.

The following categories of adults are at an increased risk of exposure to wild polioviruses:[28,31]

- Travelers to regions or countries where poliomyelitis is endemic or epidemic.
- Health-care workers in close contact with patients who may be excreting polioviruses.
- Laboratory workers handling specimens that may contain polioviruses.
- Members of communities or specific population groups with disease caused by wild polioviruses.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

IPOL vaccine should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS-Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. Immunogenicity of IPOL vaccine in individuals receiving immunoglobulin could be impaired and patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of IPV.[32]

As with any vaccine, vaccination with IPOL vaccine may not protect 100% of individuals.

Use with other vaccines: refer to **DOSAGE AND ADMINISTRATION** section for this information.

CONTRAINDICATIONS

IPOL vaccine is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including 2-phenoxyethanol, formaldehyde, neomycin, streptomycin and polymyxin B.

No further doses should be given if anaphylaxis or anaphylactic shock occurs within 24 hours of administration of one dose of vaccine.

Vaccination of persons with an acute, febrile illness should be deferred until after recovery; however, minor illness, such as mild upper respiratory infection, with or without low grade fever, are not reasons for postponing vaccine administration.

WARNINGS

Neomycin, streptomycin, polymyxin B, 2-phenoxyethanol, and formaldehyde are used in the production of this vaccine. Although purification procedures eliminate measurable amounts of these substances, traces may be present (see **DESCRIPTION** section) and allergic reactions may occur in persons sensitive to these substances (see **CONTRAINDICATIONS** section).

Systemic adverse reactions reported in infants receiving IPV concomitantly at separate sites or combined with DTP have been similar to those associated with administration of DTP alone.[11] Local reactions are usually mild and transient in nature.

Although no causal relationship between IPOL vaccine and Guillain-Barré Syndrome (GBS) has been established,[28] GBS has been temporally related to administration of another inactivated poliovirus vaccine. Deaths have been reported in temporal association with the administration of IPV (see **ADVERSE REACTIONS** section).

PRECAUTIONS

GENERAL

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity to the vaccine or similar vaccines.

Health-care providers should question the patient, parent or guardian about reactions to a previous dose of this product, or similar product.

Epinephrine Injection (1:1000) and other appropriate agents should be available to control immediate allergic reactions.

Health-care providers should obtain the previous immunization history of the vaccinee, and inquire about the current health status of the vaccinee.

Immunodeficient patients or patients under immunosuppressive therapy may not develop a protective immune response against paralytic poliomyelitis after administration of IPV.

Administration of IPOL vaccine is not contraindicated in individuals infected with HIV.[33,34,35]

Special care should be taken to ensure that the injection does not enter a blood vessel.

INFORMATION FOR PATIENTS

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their health-care provider.

The health-care provider should inform the patient, parent, or guardian of the benefits and risks of the vaccine.

The health-care provider should inform the patient, parent, or guardian of the importance of completing the immunization series.

The health-care provider should provide the Vaccine Information Statements (VISs) which are required to be given with each immunization.

DRUG INTERACTIONS

There are no known interactions of IPOL vaccine with drugs or foods. Concomitant administration, of other parenteral vaccines, with separate syringes at separate sites, is not contraindicated. The first two doses of IPOL vaccine may be administered at separate sites using separate syringes concomitantly with DTaP, acellular pertussis, *Haemophilus influenzae* type b (Hib), and hepatitis B vaccines. From historical data on the antibody responses to diphtheria, tetanus, acellular pertussis, Hib, or hepatitis B vaccines used concomitantly or in combination with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection.[11,16,36] (See **DOSAGE AND ADMINISTRATION** section.)

If IPOL vaccine has been administered to persons receiving immunosuppressive therapy, an adequate immunologic response may not be obtained. (See **PRECAUTIONS** – GENERAL section.)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential or impairment of fertility have not been conducted.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with IPOL vaccine. It is also not known whether IPOL vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. IPOL vaccine should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

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

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF IPOL VACCINE IN INFANTS BELOW SIX WEEKS OF AGE HAVE NOT BEEN ESTABLISHED.[12,20] (See **DOSAGE AND ADMINISTRATION** section.)

In the US, infants receiving two doses of IPV at 2 and 4 months of age, the seroprevalence to all three types of poliovirus was demonstrated in 95% to 100% of these infants after two doses of vaccine.[12,13]

ADVERSE REACTIONS

BODY SYSTEM AS A WHOLE

In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions at the site of injection were observed.[3] Erythema, induration and pain occurred in 3.2%, 1% and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures of ≥39°C (≥102°F) were reported in 38% of vaccinees. Other symptoms included irritability, sleepiness, fussiness, and crying. Because IPV was given in a different site but concurrently with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), these systemic reactions could not be attributed to a specific vaccine. However, these systemic reactions were comparable in frequency and severity to that reported for DTP given alone without IPV.[12] Although no causal relationship has been established, deaths have occurred in temporal association after vaccination of infants with IPV.[37]

Four additional US studies using IPOL vaccine in more than 1,300 infants,[12] between 2 to 18 months of age administered with DTP at the same time at separate sites or combined have demonstrated that local and systemic reactions were similar when DTP was given alone.

TABLE 2[12] PERCENTAGE OF INFANTS PRESENTING WITH LOCAL OR SYSTEMIC REACTIONS AT 6, 24, AND 48 HOURS OF IMMUNIZATION WITH IPOL VACCINE ADMINISTERED INTRAMUSCULARLY CONCOMITANTLY AT SEPARATE SITES WITH SANOFI[¶] WHOLE-CELL DTP VACCINE AT 2 AND 4 MONTHS OF AGE AND WITH SANOFI ACELLULAR PERTUSSIS VACCINE (TRIPEDIA®) AT 18 MONTHS OF AGE

REACTION	AGE AT IMMUNIZATION								
	2 Months (n=211)			4 Months (n=206)			18 Months[†] (n=74)		
	6 Hrs.	24 Hrs.	48 Hrs.	6 Hrs.	24 Hrs.	48 Hrs.	6 Hrs.	24 Hrs.	48 Hrs.
Local, IPOL vaccine alone[§]									
Erythema >1"	0.5%	0.5%	0.5%	1.0%	0.0%	0.0%	1.4%	0.0%	0.0%
Swelling	11.4%	5.7%	0.9%	11.2%	4.9%	1.9%	2.7%	0.0%	0.0%
Tenderness	29.4%	8.5%	2.8%	22.8%	4.4%	1.0%	13.5%	4.1%	0.0%
Systemic*									
Fever >102.2°F	1.0%	0.5%	0.5%	2.0%	0.5%	0.0%	0.0%	0.0%	4.2%
Irritability	64.5%	24.6%	17.5%	49.5%	25.7%	11.7%	14.7%	6.7%	8.0%
Tiredness	60.7%	31.8%	7.1%	38.8%	18.4%	6.3%	9.3%	5.3%	4.0%
Anorexia	16.6%	8.1%	4.3%	6.3%	4.4%	2.4%	2.7%	1.3%	2.7%
Vomiting	1.9%	2.8%	2.8%	1.9%	1.5%	1.0%	1.3%	1.3%	0.0%
Persistent Crying	Percentage of infants within 72 hours after immunization was 0.0% after dose one, 1.4% after dose two, and 0.0% after dose three.								

¶ Sanofi Pasteur Inc. formerly known as Aventis Pasteur Inc.
§ Data are from the IPOL vaccine administration site, given intramuscularly.
* The adverse reaction profile includes the concomitant use of Sanofi whole-cell DTP vaccine or Tripedia vaccine with IPOL vaccine. Rates are comparable in frequency and severity to that reported for whole-cell DTP given alone.
† Children who have been vaccinated with Tripedia vaccine.

DIGESTIVE SYSTEM
Anorexia and vomiting occurred with frequencies not significantly different as reported when DTP was given alone without IPV or OPV.[12]

NERVOUS SYSTEM
Although no causal relationship between IPOL vaccine and GBS has been established,[28] GBS has been temporally related to administration of another inactivated poliovirus vaccine.

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 and to report occurrences of certain adverse events to the US Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of that vaccine.[38,39,40]

Reporting by parents or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (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.[38,39,40]

Health-care providers also should report these events to the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION
Before administration, parenteral drug products should be checked visually for any deviation from normal appearance including container integrity. The syringe or vial and its packaging should be inspected prior to use for evidence of leakage, premature activation of the plunger, or a faulty tip seal. If evidence of such defects are observed, the syringe should not be used.

After preparation of the injection site, immediately administer IPOL vaccine intramuscularly or subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In older children and adults IPOL vaccine should be administered intramuscularly or subcutaneously in the deltoid area.

The syringe is intended for single use only, must not be reused, and must be disposed of properly and promptly following its use.

To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. If blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site.

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

Children
The primary series of IPOL vaccine consists of three 0.5 mL doses administered intramuscularly or subcutaneously, preferably eight or more weeks apart and usually at ages 2, 4, and 6 to 18 months. Under no circumstances should the vaccine be given more frequently than four weeks apart. The first immunization may be administered as early as six weeks of age. For this series, a booster dose of IPOL vaccine is administered at 4 to 6 years of age.[41]

Use with Other Vaccines
From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular pertussis, Hib, or hepatitis B vaccines used concomitantly with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection.[11,16,36] (See DRUG INTERACTIONS section.)

If the third dose of IPOL vaccine is given between 12 to 18 months of age, it may be desirable to administer this dose with Measles, Mumps, and Rubella (MMR) vaccine and/or other vaccines using separate syringes at separate sites,[28] but no data on the immunological interference between IPOL vaccine and these vaccines exist.

Use in Previously Vaccinated Children
Children and adolescents with a previously incomplete series of polio vaccine should receive sufficient additional doses of IPOL vaccine to complete the series. OPV is no longer recommended for routine immunization and is recommended only in special circumstances[7] (see **General Recommendations** section).

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

The need to routinely administer additional doses is unknown at this time.[28]

Adults
Unvaccinated Adults
A primary series of IPOL vaccine is recommended for unvaccinated adults at increased risk of exposure to poliovirus. While the responses of adults to primary series have not been studied, the recommended schedule for adults is two doses given at a 1 to 2 month interval and a third dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, three doses of IPOL vaccine should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, two doses of IPOL vaccine should be given at least 1 month apart. If less than 1 month is available, a single dose of IPOL vaccine is recommended.[28]

Incompletely Vaccinated Adults
Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose of OPV, fewer than three doses of conventional IPV or a combination of conventional IPV or OPV totaling fewer than three doses should receive at least one dose of IPOL vaccine. Additional doses needed to complete a primary series should be given if time permits.[28]

Completely Vaccinated Adults
Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a dose of IPOL vaccine.

The preferred injection site of IPOL vaccine for adults is in the deltoid area.

HOW SUPPLIED
Syringe, without needle, 0.5 mL (10 per package).
Product No. 49281-860-55

Vial, 10 Dose – Product No. 49281-860-10

CPT® Code: 90713

STORAGE
The vaccine is stable if stored in the refrigerator at 2°C to 8°C (35°F to 46°F). The vaccine must not be frozen.

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国内未承認エイズ治療薬等を用いたＨＩＶ感染症治療薬及びＨＩＶ感染症至適治療法の開発に係る応用研究

平成１７年度　総括・分担研究報告書

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