

## **ATTENUVAX®**

### **(MEASLES VIRUS VACCINE LIVE)**

#### **DESCRIPTION**

ATTENUVAX\* (Measles Virus Vaccine Live) is a live virus vaccine for vaccination against measles (rubeola).

ATTENUVAX is a sterile lyophilized preparation of a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture.

The growth medium for measles is Medium 199 (a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum) containing SPGA (sucrose, phosphate, glutamate, and human albumin) as stabilizer and neomycin.

The cells, virus pools, fetal bovine serum, and human albumin are all screened for the absence of adventitious agents. Human albumin is processed using the Cohn cold ethanol fractionation procedure.

The reconstituted vaccine is for subcutaneous administration. Each 0.5 mL dose contains not less than 1,000 TCID<sub>50</sub> (tissue culture infectious doses) of measles virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), human albumin (0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients and approximately 25 mcg of neomycin. The product contains no preservative.

Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. ATTENUVAX, when reconstituted as directed, is clear yellow.

#### **CLINICAL PHARMACOLOGY**

Measles is a common childhood disease, caused by measles virus (paramyxovirus), that may be associated with serious complications and/or death. For example, pneumonia and encephalitis are caused by measles.

The impact of measles vaccination on the natural history of each disease in the United States can be quantified by comparing the maximum number of measles cases reported in a given year prior to vaccine use to the number of cases of each disease reported in 1995. A total of 894,134 cases reported in 1941 compared to 288 cases reported in 1995 resulted in a 99.97% decrease in reported cases of measles.<sup>1</sup>

Extensive clinical trials have demonstrated that ATTENUVAX is highly immunogenic and generally well tolerated.<sup>2-6</sup> A single injection of the vaccine has been shown to induce measles hemagglutination-inhibition (HI) antibodies in 97% or more of susceptible persons. However, a small percentage (1-5%) of vaccinees may fail to seroconvert after the primary dose (see also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*).

A study<sup>7</sup> of 6 month old and 15 month old infants born to vaccine-immunized mothers demonstrated that, following vaccination with ATTENUVAX, 74% of the 6 month old infants developed detectable neutralizing antibody (NT) titers while 100% of the 15 month old infants developed NT. This rate of seroconversion is higher than that previously reported for 6 month old infants born to naturally immune mothers tested by HI assay. When the 6 month old infants of immunized mothers were revaccinated at 15 months, they developed antibody titers equivalent to the 15 month old vaccinees. The lower seroconversion rate in 6 month olds has two possible explanations: 1) Due to the limit of the detection level of the assays (NT and enzyme immunoassay [EIA]), the presence of trace amounts of undetectable maternal antibody might interfere with the seroconversion of infants; or 2) The immune system of 6 month olds is not always capable of mounting a response to measles vaccine as measured by the two antibody assays.

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There is some evidence to suggest that infants who are born to mothers who had natural measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.<sup>8,9</sup>

Efficacy of measles vaccine was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy.<sup>2,10,11</sup> These studies also established that seroconversion in response to measles vaccination paralleled protection from these diseases.<sup>12</sup>

Following vaccination, antibodies associated with protection can be measured by neutralization assays, HI, or ELISA (enzyme linked immunosorbent assay) tests. Neutralizing and ELISA antibodies to measles virus are still detectable in most individuals 11-13 years after primary vaccination.<sup>10,13</sup>

## INDICATIONS AND USAGE

### *Recommended Vaccination Schedule*

ATTENUVAX is indicated for vaccination against measles in persons 12 months of age or older.

Individuals first vaccinated with ATTENUVAX at 12 months of age or older should be revaccinated with M-M-R\* II (Measles, Mumps, and Rubella Virus Vaccine Live) prior to elementary school entry. Revaccination is intended to seroconvert those who do not respond to the first dose. The Advisory Committee on Immunization Practices (ACIP) recommends administration of the first dose of M-M-R II at 12-15 months of age and administration of the second dose of M-M-R II at 4-6 years of age.<sup>35</sup> In addition, some public health jurisdictions mandate the age for revaccination. Consult the complete text of applicable guidelines regarding routine revaccination including that of high-risk adult populations.

### *Measles Outbreak Schedule*

#### *Infants Between 6-12 Months of Age*

Local health authorities may recommend measles vaccination of infants between 6-12 months of age in outbreak situations. This population may fail to respond to the measles component of the vaccine. The younger the infant, the lower the likelihood of seroconversion (see CLINICAL PHARMACOLOGY). Such infants should receive a second dose of M-M-R II between 12 to 15 months of age followed by revaccination prior to elementary school entry.<sup>35</sup>

Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

### *Other Vaccination Considerations*

#### *Other Populations*

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps, or rubella and import these diseases into the United States. Therefore, prior to international travel, individuals known to be susceptible to one or more of these diseases can receive either a monovalent vaccine (measles, mumps or rubella), or a combination vaccine as appropriate. However, M-M-R II is preferred for persons likely to be susceptible to mumps and rubella; and if monovalent measles vaccine is not readily available, travelers should receive M-M-R II regardless of their immune status to mumps or rubella.<sup>15-17</sup>

Vaccination is recommended for susceptible individuals in high-risk groups such as college students, health care workers, and military personnel.<sup>15</sup>

According to ACIP recommendations, most persons born in 1956 or earlier are likely to have been infected with measles naturally and generally need not be considered susceptible. All children, adolescents, and adults born after 1956 are considered susceptible and should be vaccinated, if there are no contraindications. This includes persons who may be immune to measles but who lack adequate documentation of immunity such as: (1) physician-diagnosed measles, (2) laboratory evidence of measles immunity, or (3) adequate immunization with live measles vaccine on or after the first birthday.<sup>15</sup>

The ACIP recommends that "Persons vaccinated with inactivated vaccine followed within 3 months by live vaccine should be revaccinated with two doses of live vaccine. Revaccination is particularly important when the risk of exposure to natural measles virus is increased, as may occur during international travel."<sup>15</sup>

### *Post-Exposure Vaccination*

ATTENUVAX given immediately after exposure to natural measles may provide some protection if the vaccine can be administered within 72 hours of exposure. If, however, the vaccine is given a few days before exposure, substantial protection may be provided.<sup>15,18,19</sup>

### *Use With Other Vaccines*

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.

## **CONTRAINDICATIONS**

Hypersensitivity to any component of the vaccine, including gelatin.<sup>20</sup>

Do not give ATTENUVAX to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination (see PRECAUTIONS, *Pregnancy*).

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

Febrile respiratory illness or other active febrile infection. However, the ACIP has recommended that all vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper respiratory infection with or without low-grade fever, or other low-grade febrile illness.<sup>21</sup>

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;<sup>21-23</sup> cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis<sup>36</sup> (MIBE), pneumonitis<sup>37</sup> and death as a direct consequence of disseminated measles vaccine virus infection has been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

## **WARNINGS**

Due caution should be employed in administration of ATTENUVAX to persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur following vaccination (see ADVERSE REACTIONS).

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. Although there is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), no cases of transmission of CJD or viral disease have ever been identified that were associated with the use of albumin.

### *Hypersensitivity to Eggs*

Live measles vaccine is produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension and shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur (see PRECAUTIONS).<sup>25</sup>

However, the American Academy of Pediatrics (AAP) has stated, "Most children with a history of anaphylactic reactions to eggs have no untoward reactions to measles or MMR vaccine. Persons are not at increased risk if they have egg allergies that are not anaphylactic, and they should be vaccinated in the usual manner. In addition, skin testing of egg-allergic children with vaccine has not been predictive of

which children will have an immediate hypersensitivity reaction. Persons with allergies to chickens or chicken feathers are not at increased risk of reaction to the vaccine."<sup>24</sup>

#### *Hypersensitivity to Neomycin*

The AAP states, "Persons who have experienced anaphylactic reactions to topically or systemically administered neomycin should not receive measles vaccine. Most often, however, neomycin allergy manifests as a contact dermatitis, which is a delayed-type (cell-mediated) immune response rather than anaphylaxis. In such persons, an adverse reaction to neomycin in the vaccine would be an erythematous, pruritic nodule or papule, 48 to 96 hours after vaccination. A history of contact dermatitis to neomycin is not a contraindication to receiving measles vaccine."<sup>24</sup>

#### *Thrombocytopenia*

Individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia with the first dose of M-M-R II (or its component vaccines) may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases (see ADVERSE REACTIONS).

## **PRECAUTIONS**

### *General*

Adequate treatment provisions including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

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

Children and young adults who are known to be infected with human immunodeficiency viruses and are not immunosuppressed may be vaccinated. However, vaccinees who are infected with HIV should be monitored closely for vaccine-preventable diseases because immunization may be less effective than for uninfected persons (see CONTRAINDICATIONS).<sup>22,23</sup>

Vaccination should be deferred for 3 months or longer following blood or plasma transfusions, or administration of immune globulin (human).<sup>24</sup>

There are no reports of transmission of live attenuated measles virus from vaccinees to susceptible contacts.

It has been reported that attenuated measles virus vaccine live may result in a temporary depression of tuberculin skin sensitivity.<sup>24</sup> Therefore, if a tuberculin test is to be done, it should be administered either before or simultaneously with ATTENUVAX.

Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine;<sup>26</sup> no studies have been reported to date of the effect of measles virus vaccines on untreated tuberculous children. However, individuals with active untreated tuberculosis should not be vaccinated.

As for any vaccine, vaccination with ATTENUVAX may not result in protection in 100% of vaccinees.

The health care provider should determine the current health status and previous vaccination history of the vaccinee.

The health care provider should question the patient, parent or guardian about reactions to a previous dose of ATTENUVAX or other measles-containing vaccines.

### *Drug Interactions*

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.

### *Information For Patients*

The health care provider should provide the vaccine information required to be given with each vaccination to the patient, parent or guardian.

The health care provider should inform the patient, parent or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination see WARNINGS, PRECAUTIONS, ADVERSE REACTIONS.

Patients, parents or guardians should be instructed to report any serious adverse reactions to their health care provider who in turn should report such events to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.<sup>27</sup>

Pregnancy should be avoided for 3 months following vaccination, and patients should be informed of the reasons for this precaution (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*).

#### *Immunosuppressive Therapy*

The immune status of patients about to undergo immunosuppressive therapy should be evaluated so that the physician can consider whether vaccination prior to the initiation of treatment is indicated (see CONTRAINDICATIONS and PRECAUTIONS).

The ACIP has stated that "patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive live-virus vaccines. Short-term (<2 weeks), low- to moderate-dose systemic corticosteroid therapy, topical steroid therapy (e.g., nasal, skin), long-term alternate-day treatment with low to moderate doses of short-acting systemic steroid, and intra-articular, bursal, or tendon injection of corticosteroids are not immunosuppressive in their usual doses and do not contraindicate the administration of measles vaccine."<sup>15</sup>

#### *Immune Globulin*

Administration of immune globulins concurrently with ATTENUVAX may interfere with the expected immune response.<sup>15,24</sup>

See also PRECAUTIONS, *General*.

#### *Carcinogenesis, Mutagenesis, Impairment of Fertility*

ATTENUVAX has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

#### *Pregnancy*

##### *Pregnancy Category C*

Animal reproduction studies have not been conducted with ATTENUVAX. It is also not known whether ATTENUVAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware that reports have indicated that contracting natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to natural measles during pregnancy.<sup>33,34</sup> There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects.

#### *Nursing Mothers*

It is not known whether measles vaccine virus is secreted in human milk. Therefore, because many drugs are excreted in human milk, caution should be exercised when ATTENUVAX is administered to a nursing woman.

#### *Pediatric Use*

Safety and effectiveness in infants below the age of 6 months have not been established (see also CLINICAL PHARMACOLOGY).

#### *Geriatric Use*

Clinical studies of ATTENUVAX did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

### **ADVERSE REACTIONS**

The following adverse reactions are listed in decreasing order of severity, without regard to causality, within each body system category and have been reported during clinical trials, with use of the marketed vaccine, or with use of polyvalent vaccine containing measles:

#### *Body as a Whole*

Panniculitis; atypical measles; fever; syncope; headache; dizziness; malaise; irritability.

*Cardiovascular System*

Vasculitis.

*Digestive System*

Diarrhea, vomiting, nausea.

*Hemic and Lymphatic System*

Thrombocytopenia (see WARNINGS, *Thrombocytopenia*); purpura; lymphadenopathy; leukocytosis.

*Immune System*

Anaphylaxis and anaphylactoid reactions have been reported as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm in individuals with or without an allergic history.

*Musculoskeletal*

Arthralgia, myalgia.

*Nervous System*

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) (see CONTRAINDICATIONS); subacute sclerosing panencephalitis (SSPE); Guillain-Barré syndrome (GBS); febrile convulsions; afebrile convulsions or seizures; ataxia; ocular palsies.

Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine very rarely.<sup>28</sup> In no case has it been shown that reactions were actually caused by vaccine. The Centers for Disease Control and Prevention has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered".<sup>29</sup> However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per two thousand reported cases).<sup>30</sup>

Post-marketing surveillance of the more than 200 million doses of M-M-R and M-M-R II that have been distributed worldwide over 25 years (1971-1996) indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported.<sup>10</sup>

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with natural measles, 6-22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Centers for Disease Control and Prevention suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.<sup>31</sup>

*Respiratory System*

Pneumonitis (see CONTRAINDICATIONS); cough; rhinitis.

*Skin*

Stevens-Johnson syndrome; erythema multiforme; urticaria; rash.

Local reactions including burning/stinging at injection site; wheal and flare; redness (erythema); swelling; vesiculation at injection site.

*Special Senses — Ear*

Nerve deafness; otitis media.

*Special Senses — Eye*

Retinitis; optic neuritis; papillitis; retrobulbar neuritis; conjunctivitis.

*Other*

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established. No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982-1993.<sup>32</sup>

Under the National Childhood Vaccine Injury Act of 1986, health care providers and manufacturers are required to record and report certain suspected adverse events occurring within specific time periods after vaccination. However, the U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) which will accept all reports of suspected events.<sup>28</sup> A VAERS report form as well as information regarding reporting requirements can be obtained by calling VAERS 1-800-822-7967.

## DOSAGE AND ADMINISTRATION

### FOR SUBCUTANEOUS ADMINISTRATION

*Do not inject intravenously*

The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer aspect of the upper arm.

The recommended age for primary vaccination is 12 to 15 months.

Revaccination with M-M-R II is recommended prior to elementary school entry. See also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*.

Children first vaccinated when younger than 12 months of age should receive another dose between 12 to 15 months of age followed by revaccination prior to elementary school entry.<sup>35</sup> See also INDICATIONS AND USAGE, *Measles Outbreak Schedule*.

*Immune Globulin (IG) is not to be given concurrently with ATTENUVAX.*

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

*Single Dose Vial*— First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. If the lyophilized vaccine cannot be dissolved, discard. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. ATTENUVAX, when reconstituted, is clear yellow.

### *Use With Other Vaccines*

ATTENUVAX should not be given less than one month before or after administration of other live viral vaccines.

M-M-R II has been administered concurrently with VARIVAX\* [Varicella Virus Vaccine Live (Oka/Merck)], and PedvaxHIB\* [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] using separate sites and syringes. No impairment of immune response to individually tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed with M-M-R II were similar to those seen when each vaccine was given alone.

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concurrently with measles, mumps, and rubella vaccines is not recommended because there are limited data relating to the simultaneous administration of these antigens.

However, other schedules have been used. The ACIP has stated "Although data are limited concerning the simultaneous administration of the entire recommended vaccine series (i.e., DTP, OPV, MMR, and Hib vaccines, with or without hepatitis B vaccine), data from numerous studies have indicated no interference between routinely recommended childhood vaccines (either live, attenuated, or killed). These findings support the simultaneous use of all vaccines as recommended."<sup>14</sup>

## HOW SUPPLIED

No. 4589X/4309 — ATTENUVAX is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), **NDC** 0006-4589-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature.

### Storage

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or colder. Freezing during shipment will not affect potency.

Protect the vaccine from light at all times, since such exposure may inactivate the virus.

Before reconstitution, store the vial of lyophilized vaccine at 2-8°C (36-46°F) or colder. The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 2-8°C (36-46°F) and discard if not used within 8 hours.

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