ADENOVIRUS VACCINE LIVE ORAL

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Introduction

Adenovirus vaccine is used to stimulate active immunity to the adenovirus serotypes represented in the vaccine.[1]

Uses

Prevention of Adenovirus Respiratory Disease

Adenovirus type 4 and type 7 vaccine live oral (adenovirus vaccine) is used to prevent febrile acute respiratory disease caused by adenovirus type 4 and type 7.[1] The vaccine is labeled by the US Food and Drug Administration (FDA) for use in military populations 17 through 50 years of age, and is not available for use in other individuals.[1,15] Adenovirus vaccine is available in the US as adenovirus type 4 and type 7 vaccine live oral containing viable, selected strains of human adenovirus type 4 and type 7 prepared in human diploid fibroblast cell cultures.[1]

Adenoviruses, especially adenovirus type 4 and type 7, commonly cause acute respiratory disease (e.g., runny nose, fever, sore throat, breathing problems, cough, headache, croup, bronchitis).[9,12,15,105] Certain adenovirus serotypes cause other illnesses (e.g., conjunctivitis, keratoconjunctivitis, otitis media, gastroenteritis, cystitis).[9,15,105] Disseminated or life-threatening infections can occur (e.g., severe pneumonia, hepatitis, meningitis, encephalitis).[105] Adenovirus types 3, 7, and 14 have been identified in outbreaks of respiratory tract illness and can cause severe illness.[105] Infants and immunocompromised individuals are at high risk of severe adenovirus-related complications.[9,105] Adenovirus infections may occur throughout the year,[9,105] but outbreaks of adenovirus-associated respiratory disease are most common in the late winter, spring, and early summer.[9] Adenoviruses spread person to person via direct contact, respiratory droplet transmission, or food and/or water contaminated with feces.[9,15,105] Fomites also may be involved in transmission of adenoviruses since these viruses survive for long periods outside of the body, including on environmental surfaces, and are unusually stable when exposed to chemical and physical agents or adverse pH conditions.[9,105]

Military recruits are at increased risk of acute respiratory illnesses during basic training because of several factors, including close sleeping and training environments where transmission of respiratory pathogens is facilitated, congregation of young adults arriving from wide geographic distributions who may enter basic training carrying pathogens capable of being spread to others who are immunologically susceptible, and the stressful nature of basic training and military operations.[2,3,12,13] Adenoviruses, especially adenovirus type 4 and type 7, are a well documented cause of acute respiratory illness in military recruits;[2,3,12,13,15] adenoviruses reportedly cause 50–80% of cases of acute respiratory disease in this population.[3,12] Surveillance data accumulated from periods when adenovirus vaccine was not administered to military personnel indicate that the mean annual number of cases of adenovirus infection in US military recruits was approximately 13,000–15,000.[12,13] Outbreaks of adenovirus-associated disease also occur in other populations (e.g., healthcare-associated outbreaks),[3,9,105] but the combination of sustained transmission and relatively high and predictable attack rates of adenovirus-associated respiratory disease appears to be unique to military basic trainees.[3]

The US Department of Defense (DOD) recommends adenovirus vaccine for military recruits entering basic training; the vaccine also may be recommended for other military personnel at high risk for adenovirus infection.[10] Ongoing surveillance conducted by the Naval Health Research Center (NHRC) indicates that the incidence of adenovirus-related illness in military recruits dramatically decreased after the requirement that all US military recruits be vaccinated with adenovirus vaccine was reestablished in 2011.[3,13]

Clinical Experience

Safety and efficacy of adenovirus vaccine for prevention of adenovirus infection have been evaluated in a multicenter, randomized, double-blind, placebo-controlled, phase 3 study that involved 4040 US military recruits 17 years of age and older.[1,11] This study evaluated efficacy of the vaccine in preventing type 4 adenovirus-associated febrile acute respiratory disease (ARD) and inducing neutralizing antibody to adenovirus type 7.[1,11] Because the incidence of febrile ARD due to adenovirus type 7 was not anticipated to be high enough to permit a meaningful statistical assessment of the clinical effect of the type 7 vaccine component, efficacy for this component was assessed using a seroconversion end point (seroconversion defined as development of a neutralizing antibody titer of at least 1:8 on day 26 after vaccination in individuals with baseline titers less than 1:4) rather than prevention of clinical disease.[1,11] Adenovirus vaccine was 99.3% effective in preventing adenovirus type 4 febrile ARD when assessed up to 56 days after vaccination; there were no adenovirus type 4 febrile ARD cases reported in the 3031 individuals who received the vaccine, but there were 48 cases reported in the 1009 individuals who received placebo.[1,11] The seroconversion rates on day 26 after vaccination were 94.5% for adenovirus type 4 and 93.8% for adenovirus type 7.[1,11] Although no type 7 adenovirus-associated febrile or afebrile ARD cases were reported in vaccine or placebo recipients, this was expected given the estimated attack rate of adenovirus type 7 in the military base training setting at the time of the study.[1]

Dosage and Administration

■ General

Pretreatment Screening

- Perform pregnancy testing.[1]

Other General Considerations

- Defer administration of adenovirus vaccine in individuals with vomiting and/or diarrhea.[1]

■ Administration

Adenovirus vaccine is administered orally as 2 separate tablets.[1] One tablet contains the adenovirus type 4 vaccine component and one tablet contains the adenovirus type 7 vaccine component.[1]

Adenovirus vaccine tablets contain live adenovirus inside an enteric coating.[1] The tablets are designed so that they pass through the stomach intact and release live vaccine virus in the intestines.[1] The tablets should be swallowed whole and should *not* be chewed or crushed.[1] If the tablets are chewed, the adenovirus will be released too soon and could expose the upper respiratory tract to live vaccine virus and result in adenovirus disease.[1]

Store adenovirus vaccine under refrigeration between 2–8°C; do not freeze.[1] Keep the bottle tightly closed to protect from moisture and do not remove the desiccant canister from the bottle.[1]

■ Dosage

Prevention of Adenovirus Respiratory Disease

For prevention of adenovirus type 4 and type 7 respiratory disease in military personnel 17 through 50 years of age, adenovirus vaccine is administered as a single dose consisting of 2 tablets: one tablet containing the adenovirus type 4 vaccine component and one tablet containing the adenovirus type 7 vaccine component.[1]

Special Populations

> ##### Hepatic Impairment
>
> *No specific dosage recommendations.*[1]

> ##### Renal Impairment
>
> *No specific dosage recommendations.*[1]

> ##### Geriatric Patients
>
> *Adenovirus vaccine is not indicated in adults older than 50 years of age, including geriatric adults.*[1]

Cautions

Contraindications

- Pregnancy.[1]
- History of severe allergic reaction (e.g., anaphylaxis) to any vaccine component.[1]
- Inability to swallow tablets whole without chewing.[1]

Warnings/Precautions

Fetal/Neonatal Morbidity and Mortality

Natural adenovirus infection during pregnancy has been associated with fetal harm.[1] It is not known whether adenovirus vaccine can cause fetal harm when administered to pregnant women.[1]

Perform pregnancy testing prior to treatment with adenovirus vaccine.[1] The vaccine is contraindicated in pregnant women, and pregnancy should be avoided for 6 weeks after vaccination.[1]

Because vaccine recipients shed live vaccine virus for up to 28 days after vaccination and because of the possibility of fetal harm if a pregnant woman is exposed to adenovirus, vaccine recipients should be advised to use caution for 28 days after vaccination if in close contact with a pregnant woman.[1]

Altered Immunocompetence

Safety and efficacy of adenovirus vaccine have not been established in immunocompromised individuals.[1]

Shedding and Transmission

Adenovirus vaccine contains live adenoviruses that are shed in the stool of vaccine recipients and can be transmitted to and cause disease in close contacts.[1]

Because adenovirus vaccine virus is shed in the stool of vaccinees and can be transmitted, vaccinated individuals should use caution for 28 days after vaccination if they are in close contact with children younger than 7 years of age, immunocompromised individuals (e.g., patients with HIV infection or cancer, those receiving immunosuppressive therapy), or pregnant women.[1]

Human Serum Albumin

Because adenovirus vaccine contains albumin human (less than 0.3 mg of albumin in each vaccine tablet), it may carry a risk of transmitting human viruses and there is a theoretical risk of transmitting the causative agent of Creutzfeldt-Jakob disease (CJD).[1] However, improved donor screening practices and viral elimination/inactivation procedures have resulted in plasma-derived preparations with greatly reduced risk for transmission of viruses.[1] No cases of transmission of viral diseases or CJD have been identified for plasma-derived albumin human.[1]

Specific Populations

Pregnancy

Adenovirus vaccine is contraindicated in pregnant women, and pregnancy should be avoided by using effective contraception for at least 6 weeks after vaccination.[1] Females of reproductive potential should receive a pregnancy test prior to receipt of the vaccine.[1]

Naturally occurring adenovirus infection has been associated with fetal harm.[1] It is not known whether adenovirus vaccine can cause fetal harm when administered to a pregnant woman or affect reproduction capacity.[1]

There were 5 pregnancies reported among women enrolled in a clinical study that evaluated use of adenovirus vaccine in US military recruits 17 years of age and older.[1] Four of these women (3 vaccine recipients and 1 placebo recipient) were estimated to have conceived 2–13 days prior to vaccination; the other woman (vaccine recipient) conceived approximately 21 weeks after vaccination.[1] All 5 women delivered healthy infants with estimated gestational ages of 36–40 weeks.[1]

Data are not available regarding the effect of adenovirus vaccine on labor and delivery.[1] Vaccine virus shed in stools during delivery may result in transmission of the vaccine virus to the neonate.[1]

Lactation

There are no data on the presence of adenovirus vaccine in human milk, effects on milk production, or on the breastfed infant following administration.[1]

Consider the developmental and health benefits of breast-feeding along with the mother's clinical need for the vaccine and any potential adverse effects on the breast-fed infant from the vaccine or from the underlying maternal condition.[1]

Females and Males of Reproductive Potential

Adenovirus vaccine is contraindicated in pregnant women.[1] *Females of reproductive potential should receive a pregnancy test prior to treatment with the vaccine.*[1] *Advise females of reproductive potential to use effective contraception during treatment and for 6 weeks following receipt of the vaccine.*[1]

Pediatric Use

Safety and efficacy of adenovirus vaccine have not been established in infants and children younger than 17 years of age.[1]

Geriatric Use

Safety and efficacy of adenovirus vaccine have not been established in adults 65 years of age or older.[1]

Clinical studies evaluating adenovirus vaccine did not include individuals 65 years of age or older, and data are not available to determine whether geriatric individuals respond differently than younger adults.[1]

Hepatic Impairment

Pharmacokinetics of adenovirus vaccine have not been evaluated in patients with hepatic impairment.[1]

Renal Impairment

Pharmacokinetics of adenovirus vaccine have not been evaluated in patients with renal impairment.[1]

Common Adverse Effects

Adverse effects reported in 5% or more of adults 17 through 50 years of age who received adenovirus vaccine include upper respiratory tract infection, headache, nasal congestion, pharyngolaryngeal pain (sore throat), cough, arthralgia, and GI effects (abdominal pain, nausea, diarrhea, vomiting).[1]

Drug Interactions

Immunosuppressive Agents

Specific studies are not available evaluating administration of adenovirus vaccine in individuals receiving immunosuppressive therapy (e.g., alkylating agents, antimetabolites, corticosteroids, cytotoxic drugs, radiation).[1]

Individuals with altered immunocompetence (e.g., receiving immunosuppressive therapy) may be at increased risk for an adverse reaction due to uninhibited growth of live virus.[134] Such patients also may have diminished or suboptimal antibody responses to vaccines.[134]

The Centers for Disease Control and Prevention (CDC) states that high-dose corticosteroid therapy (prednisone or equivalent in a dosage at least 2 mg/kg daily or at least 20 mg daily given for at least 14 consecutive days) is considered immunosuppressive, and administration of live viral vaccines should be delayed for at least 1 month after such therapy is discontinued.[134] Short-term (less than 2 weeks); low- to moderate-dose systemic corticosteroid therapy (less than 20 mg of prednisone or equivalent daily); long-term, alternate-day systemic corticosteroid therapy using short-acting drugs; maintenance physiologic doses (replacement therapy); topical corticosteroid therapy (e.g., cutaneous, ophthalmic); corticosteroids given by inhalation; or intra-articular, bursal, or tendon injections of corticosteroids generally do not contraindicate administration of live virus vaccines.[134]

The CDC recommends that live virus vaccines generally be deferred for at least 3 months after immunosuppressive therapy is discontinued, including chemotherapy or radiation therapy for leukemia, other hematopoietic malignancies, or solid tumors, and for at least 2 months following discontinuation of anti-rejection therapies in patients after solid organ transplant.[134]

Vaccines

Although specific studies are not available evaluating whether concurrent administration of adenovirus vaccine with other vaccines affects immunologic responses or adverse effects,[1] the vaccine can be administered simultaneously with or at any interval before or after other vaccines, including other live virus vaccines.[135]

In clinical studies, adenovirus vaccine was administered concurrently with other vaccines containing diphtheria, tetanus, pertussis, hepatitis A, hepatitis B, human papillomavirus, influenza, measles, mumps, rubella, meningococcal, poliovirus, varicella, typhoid, or yellow fever antigens.[1,]

Description

Adenovirus vaccine contains live, unattenuated strains of human adenovirus type 4 and human adenovirus type 7 and is used to stimulate active immunity to the adenovirus serotypes represented in the vaccine.[1,]

Adenovirus vaccine is provided by the manufacturer as 2 separate enteric-coated tablets to be taken together: one tablet contains the adenovirus type 4 vaccine component and one tablet contains the adenovirus type 7 vaccine component.[1,] Following oral administration, the enteric-coated tablets pass through the stomach intact.[1,] The live adenoviruses are then released in the intestines where they replicate and induce active immunity in individuals with low or no preexisting neutralizing antibodies to these adenovirus serotypes.[1,]

Following a single dose of adenovirus vaccine in US military recruits 17 years of age and older, the adenovirus type 4 and type 7 seroconversion rates were 94.5 and 93.8%, respectively.[1,] Live vaccine virus is shed in the stools of individuals who receive adenovirus vaccine; fecal shedding can last for up to 28 days after vaccination.[1,] In one study, 27 or 60% of vaccinees shed adenovirus type 4 or type 7 vaccine virus, respectively, in their stools.[1,]

Adenovirus vaccine is prepared in human diploid fibroblast cell cultures (strain WI-38).[1,] The cells are grown and virus growth maintained in Dulbecco's Modified Eagle's Medium, fetal bovine serum, and sodium bicarbonate.[1,] The virus is harvested, freed of particulate cellular material by filtration, and then formulated and dried by lyophilization.[1,] The dried virus material includes monosodium glutamate, sucrose, d-mannose, d-fructose, dextrose, human serum albumin, potassium phosphate, and Plasdone® C.[1,] Each enteric-coated tablet of adenovirus type 4 and each enteric-coated tablet of adenovirus type 7 contains an inner core tablet containing anhydrous lactose, microcrystalline cellulose, polacrilin potassium, magnesium stearate, and the live adenovirus at a potency of not less than 32,000 tissue-culture infective doses (4.5 $\log_{10}$ $TCID_{50}$) per tablet.[1,] The outer tablet layer contains microcrystalline cellulose, magnesium stearate, and anhydrous lactose, with an enteric coating consisting of cellulose acetate phthalate, alcohol, acetone, and castor oil; the adenovirus type 7 tablet also contains FDC yellow #6 aluminum lake dye to differentiate it from the adenovirus type 4 tablet.[1,]

Advice to Patients

The following information contains important points for the clinician to discuss with patients during counseling. For more comprehensive monographs suitable for distribution to the patient, please refer to the *AHFS Patient Medication Information* monographs available from MedlinePlus (in English and Spanish; written at a 6th- to 8th-grade reading level).

- Prior to administration of adenovirus vaccine, provide a copy of the appropriate CDC Vaccine Information Statement (VIS) to the patient (VISs are available at [Web]).[10,]
- Advise patients to take adenovirus vaccine as directed.[1,] Advise patients to inform their clinician if not able to swallow tablets whole without chewing them.[1,]
- Advise patients that adenovirus vaccine is a live virus vaccine and that vaccine virus is shed in the stool for up to 28 days after vaccination and can be transmitted to and cause disease in close contacts during this period.[1,] To minimize the risk of transmission of vaccine virus, advise patients to take precautions (i.e., frequent hand washing, especially after bowel movements) for 28 days after vaccination if in close contact with children younger than 7 years of age, immunocompromised individuals, or pregnant women.[1,]
- Advise patients to inform their clinician of existing or contemplated concomitant therapy, including prescription and OTC drugs and dietary and herbal supplements, as well as any current illnesses (e.g., vomiting and/or diarrhea, weakened immune system).[1,]
- Advise patients to inform their clinician if they are or plan to become pregnant or are breast-feeding.[1,] Advise women to avoid pregnancy for at least 6 weeks following vaccination.[1,]
- Advise patients of other important precautionary information.[1,]

Additional Information

The American Society of Health-System Pharmacists, Inc. represents that the information provided in the accompanying monograph was formulated with a reasonable standard of care, and in conformity with professional standards in the field. Readers are advised that decisions regarding use of drugs are complex medical decisions requiring the independent, informed decision of an appropriate health care professional, and that the information contained in the monograph is provided for informational purposes only. The manufacturer's labeling should be consulted for more detailed information. The American Society of Health-System Pharmacists, Inc. does not endorse or recommend the use of any drug. The information contained in the monograph is not a substitute for medical care.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Adenovirus vaccine was developed specifically for use in military populations.[1,] The vaccine is labeled by FDA for use in military populations 17 through 50 years of age,[1,] and is not available for use in other populations.[14,]

Adenovirus Type 4 and Type 7 Vaccine Live Oral

ROUTES	FORMS	STRENGTHS	BRAND NAMES	MANUFACTURER
Oral	Tablets, enteric coated	≥4.5 $log_{10}TCID_{50}$ of adenovirus type 4 per tablet or ≥4.5 $log_{10}TCID_{50}$ of adenovirus type 7 per tablet	Adenovirus Type 4 and Type 7 Vaccine Live Oral® (copackaged in separate bottles)	

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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