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FluMist® (influenza vaccine live)

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Introduction

Influenza virus is a major cause of illness in individuals each year. On June 17, 2003, the FDA approved FluMist® (Influenza Virus Vaccine Live), the live trivalent vaccine for the prevention of influenza. FluMist® is the first influenza vaccine administered as an intranasal preparation.

Therapeutic Recommendation

FluMist® is indicated for the active immunization for the prevention of illness caused by influenza A and B viruses in healthy children and adolescents between the ages of 5-17 and in healthy adults between 18-49 years old. This vaccine may be of interest to some individuals as it is a "needle-free" alternative to the intramuscular (IM) influenza vaccine. Specific populations to benefit the most from influenza vaccination are those at risk of serious complications from the virus, including very young children, the elderly, pregnant women, and people suffering from underlying health conditions. Unfortunately, most of these populations are not included in the indication for FluMist® either due to lack of insufficient clinical studies or because of potential harm. FluMist® contains live attenuated types A and B influenza virus strains that replicate in the

nasopharynx, thus the individual vaccinated should avoid close contact with immunosuppressed persons for 21 days due to viral shedding in respiratory secretions. This limits usefulness of the nasal vaccine in healthcare workers (a population also at risk), due to the possibility of spreading the live virus to patients. Application of the vaccine directly to the respiratory mucosa offers a theoretical advantage of more closely replicating the natural infection and stimulating a mucosal IgA response that may provide better protection against variant strains. FluMist® confers protective efficacy against influenza A similar to the inactivated IM vaccine.

Dosing and Administration

The recommended dose for both adults (49 years of age or younger) and children (5 years of age or older) is 0.5 mL intranasal. Children aged 5 to 8 years who have not previously been vaccinated with influenza vaccine should receive a booster dose 60 days (plus or minus 14 days) after initial vaccination. Other patients require only one dose. The intranasal vaccine should be delivered as 0.25 mL (half the dose contained in each FluMist® sprayer) in each nostril while the patient remains in an upright position. The tip of the sprayer should be inserted just inside the nose and the plunger depressed to spray half the dose into the nostril. The sprayer is manufactured with a dose-divider clip to allow for half the dose to be administered into each nostril. FluMist® is supplied in a prefilled single-use

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sprayer that must be thawed before administration. Thawing can be achieved by holding the sprayer in the palm of the hand immediately before use or by refrigerating at 35°F to 46°F for no more than 24 hours prior to use. After thawing, FluMist® should not be refrozen. Since temperature cycling could affect product stability, storage of FluMist® in a frost-free freezer should be avoided.

Cost Comparison

FluMist® costs approximately \$50 per dose, versus \$10 per dose with the IM vaccine. If using oral medications for prophylaxis, amantadine (Symmetrel) and rimantadine (Flumadine) generally cost less than \$1 to \$2 per day, whereas oseltamivir (Tamiflu) and zanamivir (Relenza) cost approximately \$8-10 per day.

Warnings

The vaccine virus in FluMist is shed in the nares and can spread to unvaccinated contacts. Due to this risk, FluMist recipients should avoid contact with immunocompromised individuals for at least 21 days after vaccination.

Contraindications

FluMist® is an intranasal preparation, thus should not be administered parenterally. Individuals with a known hypersensitivity to eggs or egg products, especially anaphylactic reactions, should not receive FluMist®. Avoid use in children and adolescents aged 5-17 years on aspirin-containing therapy due to the association of Reye syndrome with wild-type influenza infection. Individuals with a history of Guillain-Barré syndrome, asthma, or reactive airway disease should not receive FluMist®. Individuals who may be immunosuppressed or have an altered immune status due to systemic corticosteroids, alkylating drugs, radiation, antimetabolites or other immunosuppres-

sive therapies are also contraindicated.

Special Populations

Pregnancy: Animal and human data are unavailable. FluMist® should not be administered to pregnant women since it is not known whether the fetus is harmed or reproduction capacity is affected. Pregnancy category C.

Lactation: Caution should be taken if FluMist® is administered to nursing mothers, since it is not known if FluMist® is excreted in breast milk.

Pediatrics: FluMist® should be avoided in infants and children <5 years of age since safety has yet to be established.

Geriatrics: Clinical trials did not include adults greater than 49 years of age, thus safety and efficacy have not been established.

Drug Interactions

Children or adolescents who are on aspirin-containing therapy should not receive FluMist® due to the association of Reye syndrome and wild-type influenza infection. FluMist® should be avoided in individuals on immunosuppressive therapy, such as systemic corticosteroids, alkylating drugs, radiation, antimetabolites, and other immunosuppressive therapies. Clinical studies have not been performed to evaluate the concurrent use of FluMist® with antiviral compounds that are active against influenza A and/or B viruses. However, it is suggested that FluMist® not be administered until 48 hours after the cessation of antiviral therapy. It is also advised that antiviral agents not be administered until two weeks after administration of FluMist® unless deemed medically necessary. There is no information regarding the concurrent administration of FluMist® with other intranasal preparations, including steroids. Since safety has not been determined on the concurrent administration of FluMist® with other vaccines, it is not advised for concurrent administration.

Adverse Effects

The most common effects with FluMist® include rhinorrhea, fever, sore throat, and decreased activity due to fatigue for the first couple of days after vaccination. Adverse events reported in children following their initial vaccination were rhinorrhea or nasal congestion, fever, abdominal pain, otitis media, diarrhea, decreased activity and vomiting. These symptoms were mild in severity and self-limited. Adults 18-49 years of age most commonly reported nasal congestion, rhinitis, and sinusitis.

Pharmacology

Mechanism of Action: The immune mechanisms that confer protection from influenza infection after the administration of FluMist® are not fully understood. It is



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suggested that the intranasal influenza vaccine provides immunity against the influenza virus by stimulating production of antibodies that are specific to the disease. Intranasal administration also stimulates localized mucosal antibodies and perhaps enhances cytotoxic T-cell formation. Influenza viruses are recognized by the surface antigens they carry. Hemagglutinin (H) and neuraminidase (N) are antigens that have been identified and used to classify viruses. Influenza A virus has subtypes (H1, H2, H3, N1, N2), which cause disease in humans. Immunity to the surface antigens increases resistance to the infection thus if an infection occurs there would be a decrease in the severity of the disease. The intranasal influenza vaccine might produce flu-like symptoms after vaccination of the live vaccine product; however, these symptoms should be milder than those in an unvaccinated individual.

Absorption/Distribution: Since FluMist® is administered topically as a fine mist inside the nostrils, most of the dose is deposited in the nose and nasopharynx.

Metabolism/Excretion: The exact duration of immunization after the administration of influenza vaccine is unknown, thus annual revaccination is needed.

Patient Information

1. Individuals with an allergy to eggs and egg products should not receive FluMist®.
2. Inform prescribers and pharmacists of medical conditions and medications taken.
3. FluMist® is a vaccine that is administered into the nose and is given by a health care professional in a prescriber's office, pharmacy, or a clinic.
4. Side effects from FluMist® include: chills, nasal congestion, cough, headache, fever, muscle aches, runny nose, and tiredness.
5. Close contact with individuals who have an impaired immune system should be avoided for 21 days after FluMist® administration.
6. The vaccine reduces the risk of getting the flu, but will not protect against colds or other illnesses.

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Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone combination)

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Introduction

Subutex® (buprenorphine) and Suboxone® (buprenorphine and naloxone) are Schedule III controlled substances made available in October 2002 for the treatment of opioid dependence. Only Suboxone® contains the opioid antagonist naloxone, but both Subutex® and Suboxone® contain the partial opioid agonist buprenorphine. These new sublingual formulations of naloxone and buprenorphine can be used to treat opioid dependent patients in an office setting.

Therapeutic Recommendation

The only FDA approved use for Suboxone®/Subutex® is the treatment of opioid dependency. This drug combination allows treatment in a physician office setting, which increases patient accessibility. Treatment in an office setting may allow patient avoidance of other drug users and possibly decrease the stigma associated with a "drug" clinic. Also, when buprenorphine is used with naloxone, the combination has a lower abuse potential than other current treatment options such as methadone. Because naloxone is a pure opioid antagonist and has a poor oral bioavailability, Suboxone® may produce undesirable withdrawal effects when injected, but is much less likely to do so when taken sublingually. Suboxone®/Subutex® also offer a therapeutic advantage because buprenorphine, when compared to methadone, has a favorable safety profile and a lower relapse rate in patients taking other opioids during treatment. The optimal duration of treatment for Suboxone®/Subutex® has not been established, although the length of treatment needed to prevent withdrawal symptoms is likely dependent on the duration and extent of opioid abuse.

Dosing and Administration

Subutex® is available in two different formulations, both of

which are white sublingual tablets. One tablet contains 2 mg buprenorphine and the second formulation contains 8 mg of buprenorphine. Suboxone® is available in two different formulations, the first containing 2 mg buprenorphine and 0.5 mg naloxone and the second containing 8 mg buprenorphine and 2 mg of naloxone. Both Suboxone® formulations are orange sublingual tablets. When taking these medications, the patient should place the tablet under the tongue until it is fully dissolved for optimal absorption. If the patient does not allow the tablet to dissolve and swallows the tablet, the bioavailability of the drug is decreased and the patient will not receive the adequate amount for therapeutic efficacy.

When these drugs are used together for the treatment of opioid dependence, Subutex® should be used initially since it lacks the active ingredient naloxone. This treatment dose varies depending on the time elapsed since the patient's last opioid use and the extent of opioid dependency. Subutex® should be administered to the patient on days one and two of treatment. Then on day three, Suboxone® should be substituted for Subutex® in a dose of buprenorphine equal to the dose of buprenorphine used on day two.

Suboxone® is the drug of choice for maintenance treatment. However, the patient's dose should be individualized and the maintenance dose of Suboxone® can be increased or decreased by 2 mg or 4 mg to a level controlling the patient's withdrawal. In clinical studies, Suboxone® target doses of 12 mg/day to 16 mg/day have been sufficient.

Warnings/Precautions

Respiratory Depression: Respiratory Depression can occur and even lead to death if Subutex® is not used properly or is combined with other CNS depressant drugs. Also use caution in patients already experiencing compromised respiratory function.

Dependence: Opioid dependence may result from chronic administration of buprenorphine. Withdrawal is seen with abrupt discontinuation or rapid taper, is less severe than observed with full agonists, and often presents with a delayed onset.

CNS Depression: Excessive CNS depression may result when buprenorphine is administered with other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, tranquilizers, sedative hypnotics or other CNS depressants. Concurrent administration of buprenorphine and another CNS depressant may warrant a reduction in dose of one or both agents to prevent excessive CNS depression.

Hepatic Impairment: Buprenorphine may cause or contribute to hepatic disease. Therefore, it is recommended liver function tests be performed at the initiation of treatment and then periodically thereafter.

Opioid Withdrawal Effects: Opioid withdrawal effects may be seen in patients receiving Suboxone® and dependent on opioid agonists such as heroin, morphine, or methadone.

Head Injury/ Increased Intracranial Pressure: Suboxone® and Subutex® may increase cerebrospinal pressure. Therefore, patients with head injury, intracranial lesions, or any elevation in cerebrospinal pressure should use Suboxone® and Subutex® with caution.

Allergic Reactions: Hypersensitivities to both buprenorphine and naloxone have been observed. As a result, patients with a hypersensitivity to buprenorphine should not use Suboxone® or Subutex® and patients with a hypersensitivity to naloxone should not use Suboxone®.

Cost Comparison

Drug	Cost		
	CVS	K-Mart	WalMart
Subutex® 2 mg 2 tablets (two day supply)	11.49	13.97	13.62
Suboxone® 2 mg 30 tablets (1 month supply)	103.99	86.97	89.84
Methadone® 10 mg (6 tablets=60 mg) 180 tablets (1 month supply)	299.70	239.11	193.80

The dose of methadone depends upon the patient's past opioid addiction. The dose can range anywhere from 60 mg/day to 120 mg/day.

Contraindications

Patients with a hypersensitivity to naloxone should not use Suboxone®.

Patients with a hypersensitivity to buprenorphine should not use Suboxone® or Subutex®.

Special Populations

Geriatric/Debilited Patients: Suboxone® and Subutex® should be used with caution in patients with severe impairment of hepatic, pulmonary, or renal function, myxedema, hypothyroidism, adrenal cortical insufficiency, CNS depression, coma, toxic psychoses, prostatic hypertrophy, urethral stricture, acute alcoholism, delirium tremens, or kyphoscoliosis.

Biliary Tract Dysfunction: Suboxone® and Subutex® need to be used with caution in patients with dysfunction of the biliary tract because buprenorphine can elevate intracholedochal pressure.

Pregnancy: Suboxone® and Subutex® are pregnancy category C drugs. There have been no well-controlled studies involving these drugs and only if the potential benefit outweighs the potential risk should this medication be used in pregnant women.

Pediatric use: This drug has not been studied in individuals below the age of 16 and is not recommended.

Neonatal Withdrawal: Post-marketing reports verify neonatal withdrawal symptoms from day one to day eight of life. These symptoms include convulsions, hypertonia, apnea, bradycardia, neonatal tremor, neonatal agitation and myoclonus.

Nursing Women: High doses of buprenorphine have been shown to pass through mother's milk and are therefore NOT recommended for breastfeeding mothers.

Ambulatory Patients: Caution should be used when driving or operating machinery. Patients should not engage in such activities upon drug initiation or dosage adjustment until drug outcomes affecting the ability to perform these activities are known.

Drug Interactions

Buprenorphine is metabolized by the cytochrome P-450 isozyme 3A4 (CYP 3A4). Inhibitors of CYP 3A4 such as -azole antifungals, macrolide antibiotics and HIV protease inhibitors will increase Subutex[®] and Suboxone[®] concentrations and patients receiving these medications should have their dose adjusted appropriately.

Suboxone[®]/Subutex[®] should be used with caution in patients receiving benzodiazepines or other CNS drugs due to additive CNS depression.

Adverse Effects

The most common adverse effects reported at an incidence of >1% were: headache, constipation, diaphoresis, insomnia, and nausea/vomiting. Adverse effects occurring <1% include urinary retention, orthostatic hypotension, sinus bradycardia, sinus tachycardia, blurred vision, hypertension, and nervousness or anxiety.

Pharmacology

Buprenorphine

Mechanism of Action: Buprenorphine is a partially synthetic, mixed opioid agonist-antagonist. It is believed to exert partial agonist effects at mu-opioid receptors and antagonist effects at kappa-opioid receptors. The stimulation of mu-receptors produces supraspinal analgesia, respiratory depression, euphoria, and physical dependence. Because kappa-receptor activation often generates dysphoria, buprenorphine, which is a kappa-receptor blocker, is more likely to produce euthymia than a kappa-receptor agonist. The activation of opioid receptors exerts its effects primarily through a G-protein intermediary, which thereby decreases intracellular cyclic AMP levels.

Absorption/Distribution: Buprenorphine is absorbed through the sublingual route even though oral bioavail-

ability is poor. Plasma concentrations increase in a linear fashion when compared to linear increases of the dose over the dosage range of 1-32 mg, and are not influenced to a significant degree when administered concurrently with naloxone. Buprenorphine is also highly protein bound (96%), principally to alpha and beta globulin.

Metabolism/Excretion: Buprenorphine is metabolized primarily by cytochrome P-450 isozyme 3A4. Through N-dealkylation, the active metabolite norbuprenorphine is produced. Both buprenorphine and norbuprenorphine are glucuronidated before undergoing extensive enterohepatic circulation. When given sublingually, the mean elimination half-life of buprenorphine is 37 hours. Sixty-nine percent of a buprenorphine dose is eliminated in feces while another 30% is removed by urine. The majority of buprenorphine and norbuprenorphine excreted in the urine is in the conjugated form whereas the majority of buprenorphine and norbuprenorphine eliminated in the feces is in the unconjugated form.

Naloxone

Mechanism of Action: Naloxone is a pure opioid antagonist, which competes with narcotics at opioid receptors. Naloxone antagonizes many opioid agonist effects such as analgesia, psychogenic effects, dysphoria, and miosis. Naloxone directly binds to opioid receptors but lacks intrinsic activity and prevents other narcotics from attaching to opioid receptors such as mu, kappa, delta, and sigma. Naloxone therefore can be used to diagnose opioid dependency. Since naloxone is a pure antagonist, a patient receiving naloxone will not experience opioid effects such as respiratory depression, miosis, analgesia, or sedation.

Absorption/Distribution: The quantity of naloxone in Suboxone[®] is so small that the dose proportionality cannot be measured. However, subjects receiving multiple doses show an increase in naloxone concentrations. At doses of 1 to 4 mg, mean peak levels ranged from 0.11 to 0.28 ng/ml. Naloxone is 45% protein bound and binds primarily to albumin.

Metabolism/Elimination: Naloxone is metabolized by glucuronidation into naloxone 3-glucuronide. Naloxone also undergoes N-dealkylation and reduction of the 6-oxo group. Naloxone has a short mean elimination half-life of 1.1 hours.

Patient Information

1. Educate family members/friends to notify physicians and the emergency room staff of narcotic dependence and Suboxone[®] or Subutex[®] treatment in the case of an emergency.
2. Concurrent administration of benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol with Suboxone[®] or Subutex[®] could cause serious

- overdose and death.
- Use caution when driving or operating machinery. Do not engage in such activities upon drug initiation or dosage adjustment until drug outcomes affecting the ability to perform these activities are known. Orthostatic hypotension may also result from Suboxone[®] or Subutex[®] administration.
 - Consult a physician if another prescription medication is being used or will be used in the future.

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We wish everyone
a happy and
healthy season!

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