Exemestane Tablets (Aromasin®)

Manufacturer: Pfizer Inc., Groton, CT

Indication: Exemestane is indicated for postmenopausal women with estrogen receptor–positive early breast cancer following two to three years of tamoxifen (Nolvadex®, AstraZeneca) for completion of five consecutive years of adjuvant hormonal therapy.

Drug Class: Exemestane is an aromatase inhibitor that blocks the conversion of androgens (sex hormones produced by the adrenal glands) into estrogens. The conversion process, known as aromatization, occurs mainly in a woman’s fatty tissues. Exemestane reduces the amount of estrogen in the body.

Uniqueness of Drug: Postmenopausal women with hormone receptor–positive breast cancer have several hormonal therapy options. These include tamoxifen and the newer aromatase inhibitors. In a clinical study, women taking exemestane had no cancer progression for an average of 11 months; for women taking tamoxifen, the average was seven months. This difference was statistically significant.

Warnings: Exemestane tablets may cause fetal harm when they are administered during pregnancy. Radioactivity related to 14C-exemestane crossed the placenta of rats following oral administration of 1 mg/kg of exemestane. The concentration of exemestane and its metabolites was approximately equivalent in maternal and fetal blood.

When rats were given exemestane from 14 days before mating until either day 15 or day 20 of gestation and then resumed the regimen for the 21 days of lactation, an increase in placental weight was seen at 4 mg/kg per day (about 1.5 times the recommended human daily dose based on milligrams per meter squared [mg/m²]).

Prolonged gestation and abnormal or difficult labor was observed at doses equal to or greater than 20 mg/kg per day. Increased bone resorption, a reduced number of live fetuses, decreased fetal weight, and retarded ossification were also observed at these doses.

No malformations were noted when exemestane was administered to pregnant rats during the organogenesis period at doses up to 810 mg/kg per day (approximately 320 times the recommended human dose). Daily doses of exemestane, given to rabbits during organogenesis, resulted in a decrease in placental weight at 90 mg/kg/day (about 70 times the recommended human daily dose). Abortions, increased bone resorption, and reduced fetal body weight were seen at a dose of 270 mg/kg per day.

There was no increase in the incidence of malformations in rabbits at doses up to 270 mg/kg/day (210 times the recommended human dose).

No studies have been performed in pregnant women receiving exemestane. This agent is indicated for postmenopausal women. Women who are exposed to exemestane during pregnancy should be apprised of the potential hazard to the fetus and the potential risk of loss of the pregnancy.

Precautions: Exemestane tablets should not be administered to premenopausal women or co-administered with estrogen-containing agents, which may interfere with its pharmacological action.

The pharmacokinetic parameters of exemestane were investigated in subjects with moderate or severe hepatic or renal insufficiency. Following a single 25-mg oral dose, the area-under-the-curve (AUC) concentration of exemestane was approximately three times higher than that observed in healthy volunteers.

The safety of chronic dosing in patients with moderate or severe hepatic or renal impairment has not been studied. Based on experience with exemestane at repeated doses up to 200 mg daily that demonstrated a moderate increase in non–life-threatening adverse events, dosage adjustment does not appear to be necessary.

Adverse Drug Effects: Mild-to-moderate adverse effects included hot flashes (21.2%), fatigue (16.1%), and arthralgia or bone pain (14.6%).

Dosage and Administration: The recommended dose for patients with early and advanced breast cancer is one 25-mg tablet once daily after a meal. In postmenopausal women with early breast cancer who have been treated for two to three years of tamoxifen, treatment with exemestane should continue in the absence of a recurrence or a contralateral breast cancer until completion of five years of adjuvant endocrine therapy.

Commentary: The approval of exemestane for early breast cancer was based on the Intergroup Exemestane Study. Patients who were switched to exemestane after two to three years of tamoxifen (for a combined total of five years of therapy) had 31% more protection from cancer recurrence than those who continued with tamoxifen therapy for five years.

This was an important study indicating an earlier use of oral exemestane, as opposed to the previous approval for advanced-stage breast cancer. This new indication provides women with a regimen that may significantly improve their chances of remaining free of breast cancer and recurrence, compared with the current treatment practice of five years of tamoxifen therapy.

This well-conducted clinical study, which established the superiority of switching to exemestane rather than staying with tamoxifen, prompted the National Comprehensive Cancer Network to revise its guidelines to support the use of this new switch regimen.

Sources: www.pharmacyonesource.com; www.pfizer.com/pfizer/download/uspi_aromasin.pdf

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Pharmaceutical Approval Update

**Measles, Mumps, Rubella, and Varicella Virus Vaccine Live (Proquad®)**

**Manufacturer:** Merck & Co., Inc., Whitehouse Station, NJ

**Indication:** The vaccine is indicated for simultaneous protection against measles, mumps, rubella (German measles), and varicella (chickenpox) in children 12 months to 12 years of age.

**Biological Class:** This is a combined, attenuated live virus vaccine.

**Uniqueness of Product:** This is the first vaccine approved in the U.S. to help protect against four diseases in a single injection. It is also approved for children 12 months to 12 years of age if a second dose of measles, mumps, and rubella (M-M-R) vaccine is to be administered. After 20 years of research, the product combines two Merck vaccines: M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) and Varivax® (Varicella Virus Vaccine Live, Oka/Merck).

**Warnings**

**Medical History.** Caution should be exercised in administering the vaccine product to persons with a history of cerebral injury, an individual or a family history of convulsions, or any other condition in which stress caused by fever should be avoided. The physician should be alert to the temperature elevations that may occur following vaccination.

**Rash.** A live attenuated vaccine, such as Varivax®, can result in a more extensive vaccine-associated rash or disseminated disease in individuals taking immunosuppressive drugs.

**Hypersensitivity to Eggs.** Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic or other immediate hypersensitivity reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) after ingesting eggs 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 vaccination is considered for these patients. Such individuals may be vaccinated with extreme caution. Adequate treatment should be readily available should a reaction occur.

Children with egg allergy are at low risk for anaphylactic reactions to measles-containing vaccines (including M-M-R), and skin testing of children allergic to eggs is not predictive of reactions to M-M-R vaccine. Persons with allergies to chickens or feathers do not have a higher risk of reactions to the vaccine.

**Hypersensitivity to Neomycin.** Neomycin allergy is usually manifested as a contact dermatitis. This is not a contraindication to receiving M-M-R or varicella vaccine.

**Thrombocytopenia.** No clinical data are available regarding the development or worsening of thrombocytopenia in individuals vaccinated with the product. Cases of thrombocytopenia have been reported after exposure to measles vaccine, M-M-R vaccine, and varicella vaccine.

Postmarketing experience with live M-M-R vaccine indicates that current thrombocytopenia may become more severe following vaccination. Individuals who experience thrombocytopenia after the first dose of a live M-M-R vaccine may develop thrombocytopenia with repeated doses. Serological testing for antibodies to measles, mumps, or rubella should be considered in order to determine whether additional doses of vaccine are needed. The potential risk–benefit ratio should be carefully evaluated before vaccination in such instances.

**Creutzfeld–Jakob Disease: Theoretical Risk of Transmission.** This vaccine contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk of transmission of viral diseases. Although there is a theoretical risk for transmission of Creutzfeld–Jakob disease, no case of transmission of this disease or viral disease associated with the use of albumin has been identified.

**Precautions:** The patient’s vaccination history must be obtained to determine whether there were any previous reactions to any vaccine, including the current product, Varivax®, or any M-M-R vaccines.

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use in case an anaphylactic reaction occurs.

Live attenuated vaccines can cause a more extensive vaccine-associated rash or disseminated disease in individuals taking immunosuppressive doses of corticosteroids.

The vaccine’s safety and efficacy in children and young adults with human immunodeficiency virus (HIV) infection or in individuals after exposure to measles, mumps, rubella, or varicella have not been established.

Post-licensing experience with Varivax® suggests that transmission of varicella vaccine virus may occur rarely in healthy vaccine recipients who develop a varicella-like rash and in people in contact with high-risk individuals who are susceptible to varicella, such as:

- immunocompromised individuals.
- pregnant women without a documented positive history of varicella (chickenpox) or laboratory evidence of previous infection.
- newborn infants of mothers without a documented positive history of varicella or laboratory evidence of previous infection.

Vaccine recipients should try to avoid close contact with high-risk individuals susceptible to varicella for up to six weeks following vaccination. If such contact is unavoidable, the potential risk of transmission of the varicella vaccine virus should be weighed against the risk of acquiring and transmitting wild-type varicella virus.

**Dosage and Administration:** When reconstituted, each vial of vaccine contains a single 0.5-ml dose. Children 12 months through 12 years of age should receive a single 0.5-ml dose administered subcutaneously. At least one month should elapse between a dose of a measles-containing vaccine (e.g., M-M-R® II) and a dose of vaccine. If a second dose of varicella-containing vaccine is required, at least three months should elapse between administrations of the two doses.

**Note:** Because preservatives, antiseptic agents, detergents, and other antiviral substances may inactivate the vaccine, only sterile syringes that are free of these substances should be used to reconstitute and inject the vaccine.

Prior to administration, the vaccine should be inspected before and after reconstitution for particulate matter and
Influenza Vaccine (Fluarix™)

**Manufacturer:** GlaxoSmithKline, Philadelphia, PA

**Indication:** Fluarix™ is indicated for immunization against influenza virus types A and B in adults 18 years of age and older.

**Biological Class:** The vaccine contains inactivated fragments from three different strains of the virus that causes influenza (flu). The vaccine works by provoking the body’s immune response without causing the disease.

**Uniqueness of Drug:** The vaccine contains inactivated virus.

**Warnings**

**Guillain-Barré Syndrome.** If this illness has occurred within six weeks of receiving influenza vaccine, the decision to give this vaccine or any other influenza vaccine should be based on careful consideration of the potential benefits and risks.

**Bleeding Disorders.** As with other intramuscular injectables, this vaccine should not be given to individuals with bleeding disorders (hemophilia, thrombocytopenia) or to patients receiving anticoagulant therapy unless the potential benefits outweigh the risks. If Fluarix™ is administered to such individuals, steps should be taken to avoid the risk of hematomas following the injection.

**Effectiveness.** Influenza vaccine may not protect 100% of susceptible individuals.

**Latex Allergy.** The tip cap and rubber plunger of the needle-less, prefilled syringes contain dry, natural latex rubber, which can cause allergic reactions in latex-sensitive individuals.

**Acute Illness.** The Advisory Committee on Immunization Practices has published guidelines for the vaccination of persons with recent and acute illness.

**Precautions**

**Method.** The vaccine should not be given by intravascular injection.

**Adverse Reactions.** Prior to immunization, the physician should review the patient’s health status, medical history, and immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions, and any adverse event–related signs or symptoms in order to determine whether any contraindications exist and to assess the benefits and risks of vaccination.

Appropriate medical treatment and supervision should be available in case a rare anaphylactic reaction occurs after the vaccine is given. Epinephrine injection (1:1000) and other agents used for the control of immediate allergic reactions must be immediately available.

**Sterile Procedure.** A separate sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of other infectious agents from person to person.

**Antigens.** Influenza virus is remarkable, in that minor antigenic changes occur frequently (antigenic drift), whereas a significant antigenic change leading to a pandemic change (antigenic shift) is unpredictable.

**Effectiveness.** The vaccine is not effective against all possible strains of influenza virus. Protection is limited to those strains of virus from which the vaccine is prepared and to closely related strains.

**Dosage and Administration:** The recommended dose is a single 0.5-ml injection in adults. The dose should be administered intramuscularly, preferably in the region of the deltoid muscle. Each 0.5-ml dose contains 15 mcg of hemagglutinin of each of the recommended strains in phosphate-buffered saline and other excipients, including d-alpha-tocopheryl acid succinate, traces of thimerosal (not more than 2.5 mcg per dose), formaldehyde, and gentamicin sulfate.

**Commentary:** Influenza is a serious health threat. The Food and Drug Administration (FDA) accelerated the approval of Fluarix™ to provide an adequate supply of vaccine for the American public for this year’s influenza season and years to come. The intent was that more manufacturers of influenza vaccine would be licensed in the U.S. and more vaccine dosages would be available in 2005 than in 2004, when a shortage occurred.

This is the first vaccine to be approved by the FDA’s accelerated process. The clinical benefit of Fluarix™ must now be established through the appropriate clinical trials. In studies so far, protective antibodies in the blood of adults have increased after the injection.

**Sources:** www.drugs.com/fluarix.html; http://us.gsk.com/products/assets/us_fluarix.pdf