Pharmaceutical Approval Update

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Zoster Vaccine Recombinant, Adjuvanted (Shingrix)

Manufacturer: GlaxoSmithKline Biologicals, Research Triangle Park, North Carolina

Date of Approval: October 20, 2017

Indication: Shingrix is indicated for the prevention of herpes zoster (shingles) in adults 50 years of age and older.

Drug Class: Vaccine

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Uniqueness of Drug: Reactivation of the varicella zoster virus (VZV) causes shingles. Most older adults harbor dormant VZV in their nervous system, which can reactivate with advancing age. Shingrix was developed specifically to overcome age-related immunity declines by combining the antigen glycoprotein E and the adjuvant system AS01B. There are an estimated one million cases of shingles in the U.S. each year with more than 99% of those cases occurring in adults 50 years of age or older infected with VZV. In addition, it is estimated that one in three Americans will develop shingles in their lifetime. The shingles risk increases to one in two for adults 85 years of age and older. With the approval of Shingrix, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices voted in favor of three recommendations: 1) for preventing herpes zoster and related complications for immunocompetent adults 50 years of age and older; 2) for preventing herpes zoster and related complications for immunocompetent adults who previously received Zostavax (zoster vaccine live, Merck); and 3) Shingrix is preferred over Zostavax for preventing herpes zoster and related complications. These new recommendations mean that up to 62 million more adults in the U.S. should be immunized, including about 42 million in the age range of 50–59 years and 20 million who have previously received shingles vaccination.

Warnings and Precautions:

Contraindications. This vaccine is contraindicated in patients with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the product or after a previous Shingrix dose.

Preventing and managing allergic vaccine reactions. Prior to vaccination, health care providers should review the patient's immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following Shingrix administration.

Immunosuppressive therapies. Immunosuppressive therapies may reduce the effectiveness of Shingrix.

Pediatric use. The safety and efficacy in individuals younger than the age of 18 years have not been established. Shingrix is not indicated for the prevention of primary varicella infection (chickenpox).

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Dosage and Administration: Shingrix is administered by intramuscular injection in two doses of 0.5 mL each, one at month 0 and one in months 2–6.

Commentary: The approval of Shingrix was based on phase 3 clinical trials of the vaccine's efficacy, safety, and immunogenicity involving 38,000 adults. In pooled analyses of these studies, Shingrix demonstrated greater than 90% efficacy against shingles across all age groups, as well as sustained efficacy over a follow-up period of four years. By preventing shingles, Shingrix also reduced the overall incidence of postherpetic neuralgia, the most common complication that occurs with shingles infections.

The most common adverse effects of Shingrix were pain, redness, injection-site swelling, myalgia, fatigue, headache, rigors, fever, and gastrointestinal symptoms. The majority of these reactions were transient and mild-to-moderate in intensity, lasting less than three days.

Sources: GlaxoSmithKline Biologicals, Shingrix prescribing information

Angiotensin II Injection (Giapreza)

Manufacturer: La Jolla Pharmaceutical Co., San Diego, California

Date of Approval: December 21, 2017

Indication: Angiotensin II injection is a vasoconstrictor indicated to increase blood pressure (BP) in adults with septic or other distributive shock.

Drug Class: Peptide hormone, vasoconstrictor

Uniqueness of Drug: Shock results in the inability to maintain blood flow to vital tissues, resulting in organ failure and death. Distributive shock is the most common type of shock in the inpatient setting, affecting approximately one-third of intensive care unit patients. There are approximately 800,000 distributive shock cases in the U.S. yearly; of these cases, septic shock occurs in an estimated 90% of patients. About 300,000 patients are unable to achieve an adequate BP response with current standard therapy. Angiotensin II is a naturally occurring peptide hormone of the renin–angiotensin–aldosterone system that causes vasoconstriction and increases BP. The Food and Drug Administration (FDA) priority-review approval of angiotensin II represents a major advance in the treatment of patients with septic or distributive shock.

Warnings and Precautions:

Thrombosis risk. In a double-blind, randomized, placebo-controlled study (ATHOS-3), there was a greater incidence of arterial and venous thrombotic and thromboembolic events in patients who were treated with angiotensin II than in placebo-treated patients (13% versus 5%). The major imbalance was in deep vein thromboses. Use concurrent venous thromboembolism prophylaxis in angiotensin II-treated patients.

Drug interactions. Concomitant use of angiotensin-converting enzyme inhibitors may increase the response to angiotensin II. Concomitant use of angiotensin II receptor blockers may decrease the response to angiotensin II.

Geriatric use. In ATHOS-3, 48% of the total patient population was at least 65 years of age. There were no significant differences in the safety of angiotensin II in patients older than 65 years of age compared with those younger than 65 years of age.

Dosage and Administration: Angiotensin II injection is available in 2.5 mg/mL and 5 mg/2 mL (2.5 mg/mL) vials. It must be diluted in 250–500 mL of 0.9% sodium chloride prior to use for a final concentration of 5,000 nanograms (ng)/mL or 10,000 ng/mL. The diluted solution may be stored at room temperature or under refrigeration for 24 hours. Any unused portion of an open vial should be discarded. The recommended starting dosage is 20 ng/kg per minute via continuous intravenous infusion. Administration through a central line is preferred. The BP response should be monitored and the dose titrated every five minutes by increments of up to 15 ng/kg per minute as needed to achieve or maintain the target BP. During the first three hours of treatment, do not exceed 80 ng/kg per minute. Maintenance doses should not exceed 40 ng/kg per minute. Doses as low as 1.25 ng/kg per minute may be used. Once the underlying shock has sufficiently improved, angiotensin II therapy should be downtitrated every five to 15 minutes by increments of up to 15 ng/kg per minute, based on the patient's BP.

Commentary: Angiotensin II raises BP by vasoconstriction and increased aldosterone release. The ATHOS-3 trial evaluating angiotensin II injection included 321 patients with septic or distributive shock who were randomized 1:1 to the study drug or placebo if they remained hypotensive despite fluid and vasopressor therapy. Doses were titrated to a target mean arterial pressure (MAP) of 75 mm Hg or greater during the first three hours of treatment while doses of other vasopressors were maintained. The primary endpoint was the percentage of patients who achieved either a MAP of 75 mm Hg or greater or a 10 mm Hg or greater increase in MAP without an increase in baseline vasopressor therapy at hour 3. Significantly more patients responded to angiotensin II treatment compared with placebo-treated patients. For the 114 (70%) angiotensin II-treated patients who reached the target MAP at hour 3, the median time to reach this endpoint was approximately five minutes. Angiotensin II was individually titrated to effect for each patient.

In addition to thrombotic and thromboembolic events, adverse reactions in clinical trials comparing angiotensin II with placebo included thrombocytopenia (9.8% versus 7.0%), tachycardia (8.6% versus 5.7%), fungal infection (6.1% versus 1.3%), delirium (5.5% versus 0.6%), acidosis (5.5% versus 0.6%), hyperglycemia (4.3% versus 2.5%), and peripheral ischemia (4.3% versus 2.5%).

Sources: La Jolla Pharmaceutical, Giapreza prescribing information, FDA

Glycopyrrolate Inhalation Solution (Lonhala Magnair)

Manufacturer: Sunovion Pharmaceuticals, Inc., Marlborough, Massachusetts

Date of Approval: December 5, 2017

Indication: Glycopyrrolate inhalation solution is indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

Drug Class: Long-acting antimuscarinic agent (LAMA)

Uniqueness of Drug: This is the first nebulized formulation of glycopyrrolate to receive Food and Drug Administration (FDA) approval for long-term maintenance treatment of patients with moderate-to-severe COPD. It is also the first LAMA to be sold in this dosage form. The Magnair delivery device is an almost-silent, portable, closed-system nebulizer designed to deliver the glycopyrrolate inhalation solution in two to three minutes, allowing patients to breathe normally while using the device.

Warnings and Precautions:

Contraindications. Glycopyrrolate inhalation solution is contraindicated in patients with a hypersensitivity to glycopyrrolate or any of the ingredients in the formulation.

Disease deterioration and acute episodes. Glycopyrrolate inhalation solution should not be initiated in acutely deteriorating or potentially life-threatening COPD episodes or to treat acute symptoms.

Paradoxical bronchospasm. Paradoxical bronchospasm may occur and be life threatening in patients treated with glycopyrrolate inhalation solution. If paradoxical bronchospasm occurs, glycopyrrolate inhalation solution should be immediately discontinued and patients should be treated immediately with a short-acting inhaled bronchodilator.

Immediate hypersensitivity reactions. If a patient exhibits signs that suggest an allergic reaction, immediately discontinue the drug and institute alternative treatment. Some symptoms include angioedema, urticaria, or skin rash.

Worsening of narrow-angle glaucoma. Glycopyrrolate inhalation solution should be used cautiously in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma, such as eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema. Patients should immediately inform their physician if any of these signs or symptoms develop.

Worsening of urinary retention. Glycopyrrolate inhalation solution should be used cautiously in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention, such as difficulty passing urine and painful urination, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Patients should immediately inform their physician if any of these signs or symptoms develop.

Drug interactions. Other anticholinergic agents may interact additively with glycopyrrolate inhalation solution; therefore, the combined use of these agents should be avoided.

Dosage and Administration: Glycopyrrolate inhalation solution is available as a sterile solution for inhalation in a unit-dose, single-use, 1-mL vial containing 25 mcg of glycopyrrolate. Glycopyrrolate inhalation solution is only to be used with the Magnair device. The recommended dose for maintenance treatment of COPD is one vial (25 mcg) twice daily.

Commentary: The FDA approval of glycopyrrolate inhalation solution was based on data from the Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer (GOLDEN) clinical trials program. GOLDEN-3 and GOLDEN-4 were two phase 3, 12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety trials comparing glycopyrrolate inhalation solution with placebo in adults

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with moderate to very severe COPD. At the study endpoints, glycopyrrolate-treated patients showed statistically significant and clinically important changes from baseline in trough forced expiratory volume in one second at week 12 compared with placebo-treated patients. GOLDEN-5 was a phase 3, 48-week, randomized, open-label, active-controlled, parallel-group, multicenter safety trial evaluating tolerability and long-term safety in adult patients with moderate to very severe COPD. The active comparator was tiotropium bromide (Spiriva HandiHaler, Boehringer Ingelheim). Glycopyrrolate inhalation solution was generally well tolerated in clinical studies. The most common side effects were COPD exacerbations and cough. Treatment-emergent adverse events were similar between glycopyrrolate-treated patients and tiotropium-treated patients over the study duration of GOLDEN-5.

Sources: Sunovion Pharmaceuticals, Inc., Lonhala Magnair prescribing information ■