Zoster Vaccine Recombinant, Adjuvanted

Hospital Pharmacy
2018, Vol. 53(3) 136–141

DOI: 10.1177/0018578718767103
journals.sagepub.com/home/hpx
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Generic Name: Zoster Vaccine Recombinant, Adjuvanted
Proprietary Name: *Shingrix* (GlaxoSmithKline)
Approval Rating: 1B
Therapeutic Class: Vaccines
Similar Drugs: Zoster Vaccine (Live, Attenuated)
Sound-/Look-Alike Names: Shigella Vaccine, Zoster Vaccine (Live)

Indications

Zoster vaccine recombinant, adjuvanted (*Shingrix*) is approved for the prevention of herpes zoster in patients 50 years of age and older. *Shingrix* is not indicated for the prevention of primary varicella-zoster virus (VZV) infection (chickenpox).[1]

Herpes zoster is associated with reactivation of latent VZV after infection or live virus immunization.[2,3] This reactivation commonly presents as a unilateral vesicular skin eruption arising in a single dermatome accompanied by pain that may be severe or persistent. Eruptions are often preceded by a prodrome of pain or paresthesia.[4] The most frequent complication of herpes zoster is postherpetic neuralgia, characterized by persistent pain following resolution of the rash.[3]

Clinical Pharmacology

Shingrix is a subunit vaccine consisting of a recombinant VZV envelope glycoprotein E antigen lyophilized component that is reconstituted at the time of use with $AS01_B$. The $AS01_B$ adjuvant induces a local and transient activation of the immune system by immune enhancers 3-O-desacyl-4′-monophosphoryl lipid A (MPL) (from *Salmonella minnesota*) and *Quillaja saponaria* Molina, fraction 21 (QS-21). MPL induces signals through toll-like receptor 4; QS-21's mechanism of action remains unknown, but its signaling is theorized to involve activation of the NLRP3 inflammasome complex. These 2 pathways activate antigen-presenting cells loaded with antigen in the draining lymph node, enabling recruitment of naive $CD4^+$ T cells.[5]

Shingrix is a VZV glycoprotein E purified recombinant protein antigen produced in Chinese hamster ovary cells.[1,5] The glycoprotein E component was chosen because it is the most abundant envelope glycoprotein expressed on the surface of virus-infected cells.[5] The glycoprotein E antigen is assisted by the $AS01_B$ adjuvant to induce the maximal frequencies of glycoprotein E–specific cytokine-producing $CD4^+$ T cells and the highest titers of glycoprotein E–specific antibodies.[5] The antigen remains the active ingredient and, when paired with the $AS01_B$ adjuvant, can induce strong cellular and humoral immune responses.[5] This increased reactogenicity may allow it to be used in immunocompromising diseases (ie, HIV).[2]

A small study (N = 96) evaluated the immunogenicity of *Shingrix* vaccine in adults 50 years and older with a history of herpes zoster. Mean age was 64.9 years, 65.6% were female, and 95.8% were white. All participants were seropositive for anti–glycoprotein E antibodies at baseline. One month after the second dose, 90.2% showed a vaccine response for anti–glycoprotein E antibodies, and the lowest vaccine response rate was in patients whose herpes zoster episode had occurred within the last 4 years.[6]

Pharmacokinetics

Pharmacokinetics data are not available for *Shingrix*.

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Comparative Efficacy

Indication: Prevention of Herpes Zoster and Postherpetic Neuralgia

Guidelines

Guideline: Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines
Reference: Centers for Disease Control and Prevention, 2018[7]
Comments: The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices currently recommends *Shingrix* vaccine in immunocompetent individuals 50 years and older and for those who previously received *Zostavax. Shingrix* use is recommended for individuals 50 years and older regardless of prior receipt of varicella vaccine or *Zostavax*, and does not require screening for a history of chickenpox. In addition, the Committee preferred *Shingrix* over *Zostavax* for the prevention of herpes zoster and related complications based on currently available clinical trial data. *Shingrix* vaccine effectiveness and safety will be monitored post licensure to gather additional information on rare adverse events, long-term duration of protection, adherence to the 2-dose schedule, and the effectiveness and duration of protection following one dose of the vaccine to guide further recommendations.

Studies

Drug: *Shingrix* vs Placebo
Reference: Lal H, et al, 2015 (ZOE-50 trial)[8]
Study Design: Phase 3, randomized, observer-blind, international, multicenter, placebo-controlled study
Study Funding: GlaxoSmithKline Biologicals
Patients: 15 411 adults 50 years and older. Women were included if they were of nonchildbearing potential (defined as tubal ligation, hysterectomy, ovariectomy, or postmenopause); if women were of childbearing potential, they were required to practice adequate contraception for 30 days before vaccination, during the treatment period, and for 2 months after the treatment period. Exclusion criteria included history of herpes zoster, previous vaccination against varicella or herpes zoster, an immunosuppressive condition, or chronic use of immunosuppressants or other immune-modifying drugs within 6 months prior to the first vaccine dose (prednisone less than 20 mg/day or equivalent was allowed). The majority of patients were from Europe (51.2%) and were white (71.8%) and female (61.2%). Mean age was 62.3 years.
Intervention: Subjects were randomized (1:1) to receive intramuscular injections of *Shingrix* 0.5 mL or placebo (saline 0.9% solution) at month 0 and month 2; patients were stratified according to region and age (50-59 years, 60-69 years, and 70 years and older). Starting 1 month after the administration of the second dose, participants were followed for at least 30 months through monthly contacts and annual visits, which will continue for the entire study period (expected to be approximately 60 months).

Results

Primary End Point(s)

- The overall incidence of herpes zoster per 1000 person-years was 0.3 in the *Shingrix* group and 9.1 in the placebo group, for an overall vaccine efficacy of 97.2% (95% confidence interval [CI], 93.7%-99%; $P < .001$) among participants.

Secondary End Point(s)

- There were no differences in vaccine efficacy among the stratified age groups (range, 96.6%-97.9%).
- Other secondary end points (eg, prevention of postherpetic neuralgia, impact on duration of severe pain associated with herpes zoster, mortality, and hospitalizations related to herpes zoster) were not included in this report. The study protocol requires the sister study (ZOE-70) to reach completion before secondary end points can be analyzed.
- Pain was reported as the most common injection-site reaction, occurring in 79.1% of the *Shingrix* group versus 11.2% of the placebo group. Myalgia was the most commonly reported systemic adverse reaction, occurring in 46.3% of *Shingrix* recipients compared with 12.1% of placebo recipients. Solicited and unsolicited adverse symptoms within 7 days after vaccination were reported by 84.4% of *Shingrix* patients and by 37.8% of placebo patients. To date, mean follow-up period is 3.5 years, during which time at least 1 serious adverse event occurred in 9% of participants in the *Shingrix* group and 8.9% of those receiving placebo. The most frequently reported serious adverse events in the *Shingrix* group and placebo group, respectively, were cardiac disorders (1.8% vs 1.6%), neoplasms (1.7% in both groups), and infections and infestations (1.7% vs 1.5%).

Comments: The study was conducted in 18 countries in Europe, North America, Latin America, and Asia-Australia. More than half of the study participants were women. A small (N = 129), phase 2, open-label, multicenter, single-group study conducted in the Czech Republic, Germany, Sweden, and the Netherlands found that glycoprotein E–specific cellular and humoral immune responses persisted for 6 years in healthy older adults.[3]
Limitations: The appearance of the reconstituted *Shingrix* vaccine differed from the placebo solution; however, the staff involved with the preparation and administration of the study drug did not participate in any study

assessments. Injection-site reactions would potentially be much higher with adjuvant versus saline 0.9% solution. The follow-up period has only been 3.5 years, so the long-term durability of these results remains to be proven.

Reference: Cunningham AL, et al, 2016 (ZOE-70 trial)[9]
Study Design: Phase 3, randomized, double-blind, international, multicenter, placebo-controlled study, and pooled analysis (ZOE-50 and ZOE-70)
Study Funding: GlaxoSmithKline Biologicals
Patients: 13 900 adults 70 years and older; the pooled data set (ZOE-50 and ZOE-70) consisted of 16 596 evaluable adults 70 years and older. Exclusion criteria included history of herpes zoster, previous vaccination against varicella or herpes zoster, an immunosuppressive condition, or chronic use of immunosuppressants or other immune-modifying drugs within 6 months prior to the first vaccine dose (prednisone less than 20 mg/day or equivalent was allowed). In ZOE-70, the majority of participants were from Europe (54%) and white (76.9%) and female (54.9%). Mean age was 75.6 years; 22.1% were 80 years and older.
Intervention: Subjects were randomized (1:1) to receive intramuscular injections of *Shingrix* 0.5 mL or placebo (saline 0.9% solution) at month 0 and month 2; subjects were stratified according to region and age (70-79 years vs 80 years and older). Participants were to be followed for at least 30 months after the second dose through monthly contacts and annual clinic visits.

Results

Primary End Point(s)

- The incidence rate of herpes zoster per 1000 person-years was 0.9 in the *Shingrix* group and 9.2 in the placebo group, corresponding to an overall vaccine efficacy of 89.8% (95% CI, 84.2%-93.7%; $P < .001$). Vaccine efficacy did not differ between age groups (90% for 70-79 years and 89.1% for 80 years and older).
- Pooled analysis from ZOE-50 and ZOE-70 subjects 70 years of age and older showed a vaccine efficacy of 91.3% (95% CI, 86.8%-94.5%; $P < .001$). Vaccine efficacy did not differ between age groups (91.3% for 70-79 years, and 91.4% for 80 years and older).

Secondary End Point(s)

- Incidence rate of postherpetic neuralgia per 1000 person-years in a pooled analysis of all eligible participants enrolled in ZOE-50 and ZOE-70 (50 years and older) was 0.1 in the *Shingrix* group and 0.9 in the placebo group, resulting in a vaccine efficacy of 91.2% (95% CI, 75.9%-97.7%; $P < .001$). No subjects younger than 70 years vaccinated with *Shingrix* developed postherpetic neuralgia. In the pooled analysis of subjects 70 years and older (N = 16 596), vaccine efficacy against postherpetic neuralgia was 88.8% (95% CI, 68.7%-97.1%; $P < .001$).
- During the mean follow-up period of 4 years in ZOE-70, overall rates of serious adverse effects were similar between groups (16.6% with *Shingrix* vs 17.5% with placebo). Solicited reports of reactions within 7 days after vaccination were noted in 79% of the *Shingrix* group compared with 29.5% of the placebo group. Grade 3 injection-site solicited reactions were reported in 8.5% of the *Shingrix* group and in 0.2% of the placebo group. In those receiving *Shingrix*, pain was the most commonly reported injection-site reaction (68.7%), and fatigue was the most commonly reported systemic reaction (32.9%). Most adverse reactions were transient, and the median duration was 2 to 3 days for injection-site reactions, 1 to 2 days for systemic reactions, and 1 to 2 days for grade 3 reactions.

Comments: The study was conducted in 18 countries in Europe, North America, Latin America, and Asia-Australia. The study design was the same as that of ZOE-50, and this study was conducted concurrently at the same sites so that data from the 2 studies could be pooled. The only difference was that ZOE-70 consisted only of subjects 70 years and older, resulting in different age group stratification.
Limitations: The long-term durability of vaccine response cannot be determined with an average follow-up period of 4 years.

Contraindications, Warnings, and Precautions

Contraindications

Shingrix vaccine should not be administered to individuals with a history of severe allergic reaction to a previous dose of *Shingrix* or to any component of the vaccine. Reconstituted *Shingrix* vaccine contains recombinant VZV glycoprotein E antigen, sucrose, polysorbate 80, sodium dihydrogen phosphate dehydrate, dipotassium phosphate, QS-21, MPL, liposomes (dioleoyl phosphatidylcholine [DOPC] and cholesterol), phosphate-buffered solution, disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride, and water for injection.[1]

Warnings and Precautions

Prior to vaccination with *Shingrix*, patient immunization history should be reviewed for any vaccine sensitivity and previous vaccination-related adverse reactions to mitigate any potential anaphylactic reactions following *Shingrix* administration.[1]

There are no available clinical data regarding use of *Shingrix* vaccine in pregnant women. According to the prescribing information, animal reproduction studies of *Shingrix* appear to show no adverse effects at doses lower than the recommended human dose of 0.5 mL. Male rats given a dose 20% that of a full human dose did not affect mating performance, fertility, or early embryonic development. In female rats, a dose 40% that of a full human dose was well tolerated and did not adversely affect embryofetal or pre- and postnatal survival, growth, or development of offspring.[1,5] In a reproductive toxicology study, a 200 μg/dose (4 times the human dose) of QS-21 given to rabbits resulted in maternal toxicity (reduced food consumption, reduced body weight gain) as well as reduced fetal weight and malformations in the fetus.[10]

It is unknown whether *Shingrix* is excreted in breast milk; data are not available to assess the effects of *Shingrix* on breastfeeding infants or milk production/excretion.[1]

Safety and efficacy of *Shingrix* in individuals younger than 18 years have not been established. Furthermore, *Shingrix* is not indicated for the prevention of primary varicella infection.[1]

Adverse Reactions

Overall, the vaccine was well tolerated in clinical trials, but systemic and local reactogenicity has been reported.[1,5] Subjects recorded adverse events on a standardized diary card beginning on the day of administration and continuing for 6 days after the injection. The most commonly reported local adverse reactions in recipients 50 years and older after both vaccine administrations were pain (78%), redness (38.1%), and swelling (25.9%); the most common general adverse reactions were myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%). The majority of adverse reactions had a median duration of 2 to 3 days.[1] The frequencies of adverse reactions by age group are summarized in Table 1.[1]

Unsolicited events observed at a 1.5-fold greater rate than placebo and in more than 1% of *Shingrix* recipients included chills (3.5% vs 0.2% with placebo), injection-site pruritus (2.2% vs 0.2%), malaise (1.7% vs 0.3%), arthralgia (1.7% vs 1.2%), nausea (1.4% vs 0.5%), and dizziness (1.2% vs 0.8%).[1]

The incidence of serious adverse events was similar in both *Shingrix* and placebo recipients. Up to 1 year post vaccination, serious adverse events were reported in 10.1% of *Shingrix* recipients and in 10.4% of placebo recipients. Lymphadenitis (n = 1) and fever greater than 39°C (102°F; n = 1) occurred after administration of the *Shingrix* vaccine; both cases were classified as having a causal relationship with administration of *Shingrix*. Optic ischemic neuropathy was reported in 3 *Shingrix* subjects compared with no subjects receiving placebo, yet information was insufficient to determine a causal relationship between ischemic neuropathy and administration of the vaccine.[1]

Deaths were reported during clinical trials of *Shingrix* (0.04% in the *Shingrix* group and 0.05% in the placebo group), but the causes were consistent with those generally reported in adult and elderly populations.[1]

Transient increases in C-reactive protein were observed in rabbits. Males exhibited a 9-fold increase, whereas females exhibited a 5-fold increase compared with control animals. These changes in C-reactive protein levels reflect an activation of the acute-phase response and indicate increasing levels of systemic inflammation, which may be associated with clinical adverse events (ie, malaise, fatigue).[5]

The frequencies of solicited local and general adverse events in subjects 70 years and older were lower than in younger adults (50 through 69 years) (see Table 1). The median duration of adverse reactions was 2 to 3 days.[1]

Drug Interactions

The effectiveness of *Shingrix* may be reduced in patients receiving immunosuppressive therapies.[1]

Recommended Monitoring

Monitor for anaphylaxis and syncope for 15 minutes following administration.[11] If seizure-like activity associated with syncope occurs, maintain patient in supine or Trendelenburg position to reestablish adequate cerebral perfusion.[1]

Dosing

In adults 50 years and older, the recommended vaccination regimen involves the administration of 2 intramuscular injections of zoster vaccine recombinant, adjuvanted (0.5 mL each); the first dose is given during the first office visit, and the second dose is given 2 to 6 months after the initial dose.[1]

Preparation of *Shingrix* requires reconstitution of the lyophilized glycoprotein E antigen powder with the provided $AS01_B$ adjuvant suspension. After the vial caps have been removed, each vial top should be cleansed; then the liquid adjuvant should be drawn into a syringe and injected slowly into the lyophilized glycoprotein E antigen vial. The vial should be gently shaken to thoroughly mix the adjuvant and glycoprotein E antigen until the powder is completely dissolved. The reconstituted suspension should be administered immediately, but can be refrigerated between 2°C and 8°C (36°F and 46°F) and used within 6 hours. Discard reconstituted vaccine if not used within 6 hours.[1,5]

The dose of the reconstituted *Shingrix* vaccine is 0.5 mL (50 μg of the recombinant glycoprotein E antigen, 50 μg of MPL, and 50 μg of QS-21) and is for intramuscular injection. The preferred site of intramuscular injection is the deltoid region of the upper arm.[1]

Table 1. Incidence of Adverse Reactions Within 7 Days of Shingrix Administration (Modified Intention-to-Treat Cohort) in ZOE-50 and ZOE-70 Trials.[1]

	50-59 years		60-69 years		≥70 years	
	Shingrix	Placebo[a]	*Shingrix*	Placebo[a]	*Shingrix*	Placebo[a]
Local adverse reactions	n = 1315	n = 1312	n = 1311	n = 1305	n = 2258	n = 2263
Pain	88.4%	14.4%	82.8%	11.1%	69.2%	8.8%
Redness	38.7%	1.2%	38.4%	1.6%	37.7%	1.2%
Swelling	30.5%	0.8%	26.5%	1%	23%	1.1%
General adverse reactions	n = 1315	n = 1312	n = 1309	n = 1305	n = 2252	n = 2264
Myalgia	56.9%	15.2%	49%	11.2%	35.1%	9.9%
Fatigue	57%	19.8%	45.7%	16.8%	36.6%	14.4%
Headache	50.6%	21.6%	39.6%	15.6%	29%	11.8%
Shivering	35.8%	7.4%	30.3%	5.7%	19.5%	4.9%
Fever	27.8%	3%	23.9%	3.4%	14.3%	2.7%
Gastrointestinal effects (nausea, vomiting, diarrhea, and/or abdominal pain)	24.3%	10.7%	16.7%	8.7%	13.5%	7.6%

[a]Placebo = saline solution.

There is no immunogenicity difference between subjects who received the second dose of the vaccine at 2 months and those who received it at 6 months.[1,12]

Shingrix administered with unadjuvanted seasonal influenza vaccine is well tolerated and did not affect overall efficacy of the vaccines.[13] However, no studies have been conducted to determine the safety and efficacy of same-day administration of *Shingrix* and an adjuvanted influenza vaccine.

Product Availability

Shingrix is available as a copackage that includes a single-dose 50-µg vial of lyophilized recombinant VZV glycoprotein E antigen, and a single-dose vial of $AS01_B$ adjuvant comprised of 50 µg each of QS-21 and MPL immune enhancers combined with liposomal suspension components.[1,5,14] *Shingrix* is supplied as a single-dose package containing 1 vial of $AS01_B$ adjuvant and 1 vial of lyophilized glycoprotein E antigen, and as a multidose package containing 10 vials each of $AS01_B$ adjuvant and lyophilized glycoprotein E antigen.[1,5] The lyophilized glycoprotein E antigen vial caps are brown and adjuvant vial caps are blue-green.[1,5]

The glycoprotein E antigen is a white powder containing 50 µg of glycoprotein E, 20 mg of sucrose, 0.8 mg of polysorbate 80, 0.16 mg of sodium dihydrogen phosphate dehydrate, and 0.116 mg of dipotassium phosphate lyophilized from a fill volume of 0.5 mL in a single 3-mL glass vial closed with a rubber stopper that does not contain natural rubber latex.[1,5]

$AS01_B$ adjuvant is an opalescent, colorless to pale brownish liquid suspension provided in a 3-mL glass vial closed with a rubber stopper that does not contain natural rubber latex. The $AS01_B$ adjuvant vial does not contain any drug substance, but is composed of 50 µg of QS-21, 50 µg of MPL, liposomes (1 mg of DOPC and 250 µg of cholesterol per 0.5 mL dose), and phosphate-buffered solution containing disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride, and water for injection.[1,5]

There is no preservative in either vial of lyophilized glycoprotein E antigen powder or $AS01_B$ adjuvant suspension. Traces of host cell proteins (3% or less) and DNA (2.1 pg or less) may be present from the manufacturing process.[1,5]

Shingrix and $AS01_B$ adjuvant should be refrigerated between 2°C and 8°C (36°F and 46°F).[1,14] The product expires 36 months after the manufacturer filling date.[14] Both adjuvant and lyophilized glycoprotein E antigen should never be frozen. If freezing occurs, all frozen components should be discarded.[1]

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

No REMS is required for *Shingrix*.[14]

Conclusion

Shingrix is a new vaccine against herpes zoster that can provide greater vaccine efficacy than the older herpes zoster vaccine *Zostavax*. Approval of *Shingrix* expands access to adults 50 years and older; *Zostavax* guidelines recommended use in those 60 years and older. Overall, the *Shingrix* vaccine was well tolerated, and when severe effects did occur, they were transient and resolved after 2 to 3 days. Many questions exist regarding the durability and duration of protection of *Shingrix*. Pivotal studies are ongoing, and longer term data are still being collected, but the durability of response appears to be good.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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