

SHINGRIX- zoster vaccine recombinant, adjuvanted

A-S Medication Solutions

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SHINGRIX safely and effectively. See full prescribing information for SHINGRIX.

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted), suspension for intramuscular injection

Initial U.S. Approval: 2017

-----RECENT MAJOR CHANGES-----

Warnings and Precautions, Guillain-Barré syndrome (5.2)

03/2021

-----INDICATIONS AND USAGE-----

SHINGRIX is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older.

Limitations of Use (1):

- SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

-----DOSAGE AND ADMINISTRATION-----

For intramuscular administration only.

Administer 2 doses (0.5 mL each) at 0 and 2 to 6 months. (2.2, 2.3)

-----DOSAGE FORMS AND STRENGTHS-----

Suspension for injection supplied as a single-dose vial of lyophilized varicella zoster virus glycoprotein E (gE) antigen component to be reconstituted with the accompanying vial of AS01_B adjuvant suspension component. After reconstitution, a single dose of SHINGRIX is 0.5 mL. (3)

-----CONTRAINDICATIONS-----

History of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX. (4)

-----WARNINGS AND PRECAUTIONS-----

In a postmarketing observational study, an increased risk of Guillain-Barré syndrome was observed during the 42 days following vaccination with SHINGRIX. (5.2, 6.2)

-----ADVERSE REACTIONS-----

- Solicited local adverse reactions in subjects aged 50 years and older were pain (78.0%), redness (38.1%), and swelling (25.9%). (6.1)
- Solicited general adverse reactions in subjects aged 50 years and older were myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SHINGRIX is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older.

Limitations of Use:

- SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Reconstitution

SHINGRIX is supplied in 2 vials that must be combined prior to administration. Prepare SHINGRIX by reconstituting the lyophilized varicella zoster virus glycoprotein E (gE) antigen component (powder) with the accompanying AS01_B adjuvant suspension component (liquid). Use only the supplied adjuvant suspension component (liquid) for reconstitution. The reconstituted vaccine should be an opalescent, colorless to pale brownish liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

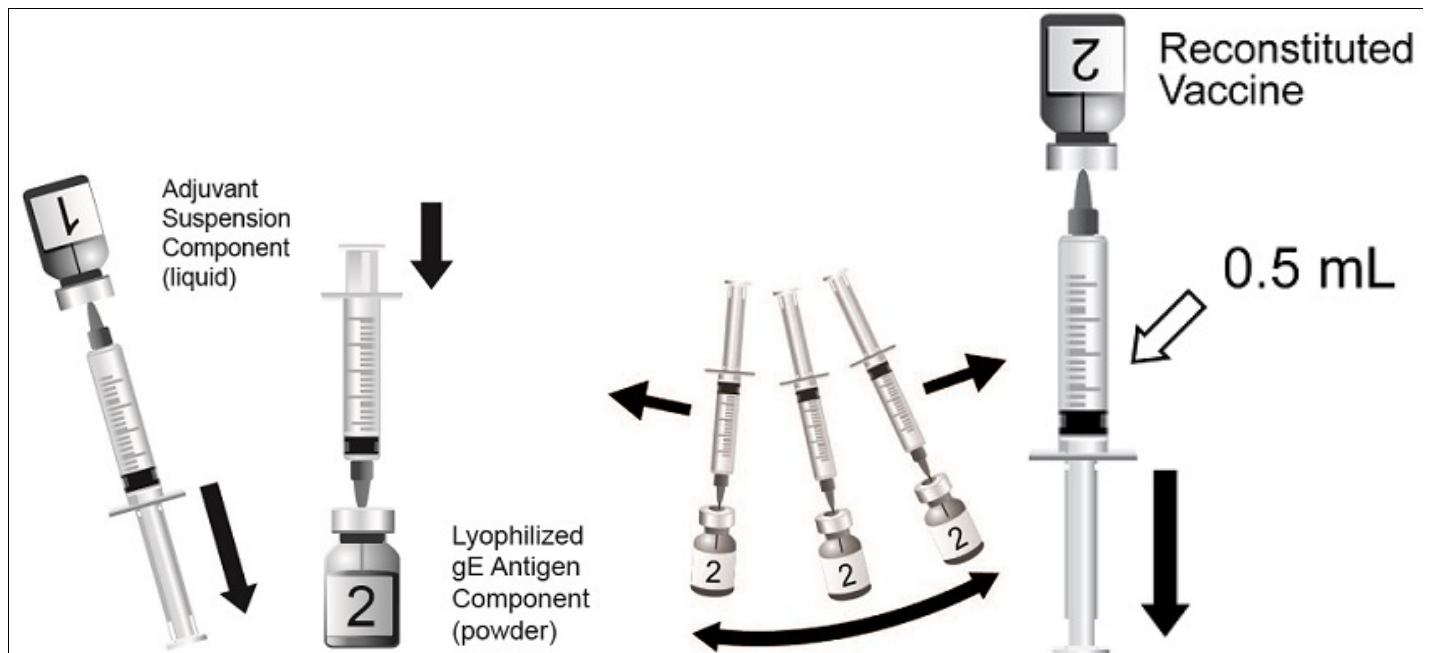


Figure 1. Cleanse both vial stoppers. Using a sterile needle and sterile syringe, withdraw the entire contents of the vial containing the adjuvant suspension component (liquid) by slightly tilting the vial. Vial 1 of 2.

Figure 2. Slowly transfer entire contents of lyophilized gE antigen component vial (powder). Vial 2 of 2.

Figure 3. Gently shake the vial to thoroughly mix contents until powder is completely dissolved.

Figure 4. After reconstitution, withdraw 0.5 mL from the vial containing the reconstituted vaccine and administer **intramuscularly**.

2.2 Administration Instructions

For intramuscular injection only.

After reconstitution, administer SHINGRIX immediately or store refrigerated between 2° and 8°C (36° and 46°F) and use within 6 hours. Discard reconstituted vaccine if not used within 6 hours.

Use a separate sterile needle and sterile syringe for each individual. The preferred site for intramuscular injection is the deltoid region of the upper arm.

2.3 Dose and Schedule

Two doses (0.5 mL each) administered intramuscularly according to the following schedule: A first dose at Month 0 followed by a second dose administered anytime between 2 and 6 months later.

3 DOSAGE FORMS AND STRENGTHS

SHINGRIX is a suspension for injection supplied as a single-dose vial of lyophilized gE antigen component to be reconstituted with the accompanying vial of AS01_B adjuvant suspension component. A single dose after reconstitution is 0.5 mL.

4 CONTRAINDICATIONS

Do not administer SHINGRIX to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX [see Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the 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 administration of SHINGRIX.

5.2 Guillain- Barré Syndrome (GBS)

In a postmarketing observational study, an increased risk of GBS was observed during the 42 days following vaccination with SHINGRIX [see Adverse Reactions (6.2)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of SHINGRIX could reveal adverse reactions not observed in clinical trials.

Overall, 17,041 adults aged 50 years and older received at least 1 dose of SHINGRIX in

17 clinical studies.

The safety of SHINGRIX was evaluated by pooling data from 2 placebo-controlled clinical studies (Studies 1 and 2) involving 29,305 subjects aged 50 years and older who received at least 1 dose of SHINGRIX (n = 14,645) or saline placebo (n = 14,660) administered according to a 0- and 2-month schedule. At the time of vaccination, the mean age of the population was 69 years; 7,286 (24.9%) subjects were aged 50 to 59 years, 4,488 (15.3%) subjects were aged 60 to 69 years, and 17,531 (59.8%) subjects were aged 70 years and older. Both studies were conducted in North America, Latin America, Europe, Asia, and Australia. In the overall population, the majority of subjects were white (74.3%), followed by Asian (18.3%), black (1.4%), and other racial/ethnic groups (6.0%); 58% were female.

Solicited Adverse Events

In Studies 1 and 2, data on solicited local and general adverse events were collected using standardized diary cards for 7 days following each vaccine dose or placebo (i.e., day of vaccination and the next 6 days) in a subset of subjects (n = 4,886 receiving SHINGRIX, n = 4,881 receiving placebo with at least 1 documented dose). Across both studies, the percentages of subjects aged 50 years and older reporting each solicited local adverse reaction and each solicited general adverse event following administration of SHINGRIX (both doses combined) were pain (78.0%), redness (38.1%), and swelling (25.9%); and myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%), respectively.

The reported frequencies of specific solicited local adverse reactions and general adverse events (overall per subject), by age group, from the 2 studies are presented in Table 1.

Table 1. Percentage of Subjects with Solicited Local Adverse Reactions and General Adverse Events within 7 Days^a of Vaccination in Adults Aged 50 to 59 Years, 60 to 69 Years, and 70 Years and Older^b (Total Vaccinated Cohort with 7-Day Diary Card)

	Aged 50 - 59 Years		Aged 60 - 69 Years		Aged ≥70 Years	
	SHINGRIX %	Placebo ^c %	SHINGRIX %	Placebo ^c %	SHINGRIX %	Placebo ^c %
Local Adverse Reactions	n = 1,315	n = 1,312	n = 1,311	n = 1,305	n = 2,258	n = 2,263
Pain	88.4	14.4	82.8	11.1	69.2	8.8
Pain, Grade 3 ^d	10.3	0.5	6.9	0.5	4.0	0.2
Redness	38.7	1.2	38.4	1.6	37.7	1.2
Redness, >100 mm	2.8	0.0	2.6	0.0	3.1	0.0
Swelling	30.5	0.8	26.5	1.0	23.0	1.1
Swelling, >100 mm	1.1	0.0	0.5	0.0	1.3	0.0

General Adverse Events	n = 1,315	n = 1,312	n = 1,309	n = 1,305	n = 2,252	n = 2,264
Myalgia	56.9	15.2	49.0	11.2	35.1	9.9
Myalgia, Grade 3 ^e	8.9	0.9	5.3	0.8	2.8	0.4
Fatigue	57.0	19.8	45.7	16.8	36.6	14.4
Fatigue, Grade 3 ^e	8.5	1.8	5.0	0.8	3.5	0.8
Headache	50.6	21.6	39.6	15.6	29.0	11.8
Headache, Grade 3 ^e	6.0	1.7	3.7	0.2	1.5	0.4
Shivering	35.8	7.4	30.3	5.7	19.5	4.9
Shivering, Grade 3 ^e	6.8	0.2	4.5	0.3	2.2	0.3
Fever	27.8	3.0	23.9	3.4	14.3	2.7
Fever, Grade 3 ^f	0.4	0.2	0.5	0.2	0.1	0.1
GI ^g	24.3	10.7	16.7	8.7	13.5	7.6
GI, Grade 3 ^e	2.1	0.7	0.9	0.6	1.2	0.4

Total vaccinated cohort for safety included all subjects with at least 1 documented dose (n).

^a 7 days included day of vaccination and the subsequent 6 days.

^b Data for subjects aged 50 to 59 years and 60 to 69 years are based on Study 1. Data for subjects 70 years and older are based on pooled data from Study 1: NCT01165177 and Study 2: NCT01165229.

^c Placebo was a saline solution.

^d Grade 3 pain: Defined as significant pain at rest; prevents normal everyday activities.

^e Grade 3 myalgia, fatigue, headache, shivering, GI: Defined as preventing normal activity.

^f Fever defined as $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ for oral, axillary, or tympanic route, or $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$ for rectal route; Grade 3 fever defined as $> 39.0^{\circ}\text{C}/102.2^{\circ}\text{F}$.

^g GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain.

The incidence of solicited local and general symptoms was lower in subjects aged 70 years and older compared with those aged 50 to 69 years.

The majority of solicited local adverse reactions and general adverse events seen with SHINGRIX had a median duration of 2 to 3 days.

There were no differences in the proportions of subjects reporting any or Grade 3 solicited local reactions between Dose 1 and Dose 2. Headache and shivering were reported more frequently by subjects after Dose 2 (28.2% and 21.4%, respectively)

compared with Dose 1 (24.4% and 13.8%, respectively). Grade 3 solicited general adverse events (headache, shivering, myalgia, and fatigue) were reported more frequently by subjects after Dose 2 (2.3%, 3.1%, 3.6%, and 3.5%, respectively) compared with Dose 1 (1.4%, 1.4%, 2.3%, and 2.4%, respectively).

Unsolicited Adverse Events

Unsolicited adverse events that occurred within 30 days following each vaccination (Day 0 to 29) were recorded on a diary card by all subjects. In the 2 studies, unsolicited adverse events occurring within 30 days of vaccination were reported in 50.5% and 32.0% of subjects who received SHINGRIX (n = 14,645) and placebo (n = 14,660), respectively (Total Vaccinated Cohort). Unsolicited adverse events that occurred in $\geq 1\%$ of recipients of SHINGRIX and at a rate at least 1.5-fold higher than placebo included chills (3.5% versus 0.2%), injection site pruritus (2.2% versus 0.2%), malaise (1.7% versus 0.3%), arthralgia (1.7% versus 1.2%), nausea (1.4% versus 0.5%), and dizziness (1.2% versus 0.8%).

Gout (including gouty arthritis) was reported by 0.18% (n = 27) versus 0.05% (n = 8) of subjects who received SHINGRIX and placebo, respectively, within 30 days of vaccination; available information is insufficient to determine a causal relationship with SHINGRIX.

Serious Adverse Events (SAEs)

In the 2 studies, SAEs were reported at similar rates in subjects who received SHINGRIX (2.3%) and placebo (2.2%) from the first administered dose up to 30 days post last vaccination. SAEs were reported for 10.1% of subjects who received SHINGRIX and for 10.4% of subjects who received placebo from the first administered dose up to 1 year post last vaccination. One subject (<0.01%) reported lymphadenitis and 1 subject (<0.01%) reported fever greater than 39°C; there was a basis for a causal relationship with SHINGRIX.

Optic ischemic neuropathy was reported in 3 subjects (0.02%) who received SHINGRIX (all within 50 days after vaccination) and 0 subjects who received placebo; available information is insufficient to determine a causal relationship with SHINGRIX.

Deaths

From the first administered dose up to 30 days post last vaccination, deaths were reported for 0.04% of subjects who received SHINGRIX and 0.05% of subjects who received placebo in the 2 studies. From the first administered dose up to 1 year post last vaccination, deaths were reported for 0.8% of subjects who received SHINGRIX and for 0.9% of subjects who received placebo. Causes of death among subjects were consistent with those generally reported in adult and elderly populations.

Potential Immune-Mediated Diseases

In the 2 studies, new onset potential immune-mediated diseases (pIMDs) or exacerbation of existing pIMDs were reported for 0.6% of subjects who received SHINGRIX and 0.7% of subjects who received placebo from the first administered dose up to 1 year post last vaccination. The most frequently reported pIMDs occurred with comparable frequencies in the group receiving SHINGRIX and the placebo group.

Dosing Schedule

In an open-label clinical study, 238 subjects 50 years and older received SHINGRIX as a

0- and 2-month or 0- and 6-month schedule. The safety profile of SHINGRIX was similar when administered according to a 0- and 2-month or 0- and 6-month schedule and was consistent with that observed in Studies 1 and 2.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of SHINGRIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

General Disorders and Administration Site Conditions

Decreased mobility of the injected arm which may persist for 1 or more weeks.

Immune System Disorders

Hypersensitivity reactions, including angioedema, rash, and urticaria.

Nervous System Disorders

Guillain-Barré syndrome.

Postmarketing Observational Study of the Risk of Guillain-Barré Syndrome following Vaccination with SHINGRIX

The association between vaccination with SHINGRIX and GBS was evaluated among Medicare beneficiaries aged 65 years or older. Using Medicare claims data, from October 2017 through February 2020, vaccinations with SHINGRIX among beneficiaries were identified through National Drug Codes, and potential cases of hospitalized GBS among recipients of SHINGRIX were identified through International Classification of Diseases codes.

The risk of GBS following vaccination with SHINGRIX was assessed in self-controlled case series analyses using a risk window of 1 to 42 days post-vaccination and a control window of 43 to 183 days post-vaccination. The primary analysis (claims-based, all doses) found an increased risk of GBS during the 42 days following vaccination with SHINGRIX, with an estimated 3 excess cases of GBS per million doses administered to adults aged 65 years or older. In secondary analyses, an increased risk of GBS was observed during the 42 days following the first dose of SHINGRIX, with an estimated 6 excess cases of GBS per million doses administered to adults aged 65 years or older, and no increased risk of GBS was observed following the second dose of SHINGRIX. These analyses of GBS diagnoses in claims data were supported by analyses of GBS cases confirmed by medical record review. While the results of this observational study suggest a causal association of GBS with Shingrix, available evidence is insufficient to establish a causal relationship.

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

For concomitant administration of SHINGRIX with inactivated influenza vaccine [*see Clinical Studies (14.5)*].

7.2 Immunosuppressive Therapies

Immunosuppressive therapies may reduce the effectiveness of SHINGRIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no available human data to establish whether there is vaccine-associated risk with SHINGRIX in pregnant women.

A reproductive and developmental toxicity study was performed in female rats administered SHINGRIX or the AS01_B adjuvant alone prior to mating, during gestation, and during lactation. The total dose was 0.2 mL on each occasion (a single human dose of SHINGRIX is 0.5 mL). This study revealed no adverse effects on fetal or pre-weaning development due to SHINGRIX (see *Data*).

Data

Animal Data: In a reproductive and developmental toxicity study, female rats were administered SHINGRIX or the AS01_B adjuvant alone by intramuscular injection 28 and 14 days prior to mating, on gestation Days 3, 8, 11, and 15, and on lactation Day 7. The total dose was 0.2 mL on each occasion (a single human dose of SHINGRIX is 0.5 mL). No adverse effects on pre-weaning development up to post-natal Day 25 were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known whether SHINGRIX is excreted in human milk. Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SHINGRIX and any potential adverse effects on the breastfed child from SHINGRIX or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness in individuals younger than 18 years have not been established. SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

8.5 Geriatric Use

Of the total number of subjects who received at least 1 dose of SHINGRIX in the 2 efficacy trials (n = 14,645), 2,243 (15.3%) were aged 60 to 69 years, 6,837 (46.7%) were aged 70 to 79 years, and 1,921 (13.1%) were 80 years and older. There were no

clinically meaningful differences in efficacy across the age groups or between these subjects and younger subjects. [See *Clinical Studies (14.1, 14.2, 14.3).*]

The frequencies of solicited local and general adverse events in subjects aged 70 years and older were lower than in younger adults (aged 50 through 69 years). [See *Adverse Reactions (6.1).*]

11 DESCRIPTION

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted) is a sterile suspension for intramuscular injection. The vaccine is supplied as a vial of lyophilized recombinant varicella zoster virus surface glycoprotein E (gE) antigen component, which must be reconstituted at the time of use with the accompanying vial of AS01_B adjuvant suspension component. The lyophilized gE antigen component is presented in the form of a sterile white powder. The AS01_B adjuvant suspension component is an opalescent, colorless to pale brownish liquid supplied in vials.

The gE antigen is obtained by culturing genetically engineered Chinese Hamster Ovary cells, which carry a truncated gE gene, in media containing amino acids, with no albumin, antibiotics, or animal-derived proteins. The gE protein is purified by several chromatographic steps, formulated with excipients, filled into vials, and lyophilized.

The adjuvant suspension component is AS01_B which is composed of 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* and QS-21, a saponin purified from plant extract *Quillaja saponaria* Molina, combined in a liposomal formulation. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol in phosphate-buffered saline solution containing disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride, and water for injection.

After reconstitution, each 0.5-mL dose is formulated to contain 50 mcg of the recombinant gE antigen, 50 mcg of MPL, and 50 mcg of QS-21. Each dose also contains 20 mg of sucrose (as stabilizer), 4.385 mg of sodium chloride, 1 mg of DOPC, 0.54 mg of potassium dihydrogen phosphate, 0.25 mg of cholesterol, 0.160 mg of sodium dihydrogen phosphate dihydrate, 0.15 mg of disodium phosphate anhydrous, 0.116 mg of dipotassium phosphate, and 0.08 mg of polysorbate 80. After reconstitution, SHINGRIX is a sterile, opalescent, colorless to pale brownish liquid.

SHINGRIX does not contain preservatives. Each dose may also contain residual amounts of host cell proteins ($\leq 3.0\%$) and DNA (≤ 2.1 picograms) from the manufacturing process.

The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The risk of developing herpes zoster (HZ) increases with age and appears to be related to a decline in VZV-specific immunity. SHINGRIX was shown to boost VZV-specific immune response, which is thought to be the mechanism by which it protects against zoster disease [see *Clinical Studies (14)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

SHINGRIX has not been evaluated for its carcinogenic or mutagenic potential. Vaccination of female rats with SHINGRIX had no effect on fertility [see *Use in Specific Populations (8.1)*]. In a male fertility study, rats were vaccinated with 0.1 mL of SHINGRIX (a single human dose is 0.5 mL) on 42, 28, and 14 days prior to mating. There were no effects on male fertility.

14 CLINICAL STUDIES

14.1 Efficacy in Subjects 50 Years and Older

Study 1 was a randomized, placebo-controlled, observer-blind clinical study conducted in 18 countries. Randomization was stratified (8:5:3:1) by age: 50 to 59 years, 60 to 69 years, 70 to 79 years, and ≥ 80 years. The study excluded, among others, subjects who were immunocompromised, had a history of previous HZ, were vaccinated against varicella or HZ, and patients whose survival was not expected to be at least 4 years or with conditions that might interfere with study evaluations. Subjects were followed for the development of HZ and postherpetic neuralgia (PHN) for a median of 3.1 years (range: 0 to 3.7 years). Suspected HZ cases were followed prospectively for the development of PHN, an HZ-related complication defined as HZ-associated pain (rated as 3 or greater on a 0- to 10-point scale by the study subject) occurring or persisting at least 90 days following the onset of rash in confirmed cases of HZ.

The primary efficacy analysis population (referred to as the modified Total Vaccinated Cohort [mTVC]) included 14,759 subjects aged 50 years and older who received 2 doses (0 and 2 months) of either SHINGRIX (n = 7,344) or placebo (n = 7,415) and did not develop a confirmed case of HZ within 1 month after the second dose. In the mTVC population, 61.2% were female; 72.3% were white, 18.9% were Asian, 1.7% were black, and 7.0% were of other racial/ethnic groups. The mean age of subjects was 62.3 years.

Confirmed HZ cases were determined by either Polymerase Chain Reaction (PCR) (89.4%) or by a Clinical Evaluation Committee (10.6%).

Efficacy against Herpes Zoster

Compared with placebo, SHINGRIX significantly reduced the risk of developing HZ by 97.2% (95% CI: 93.7, 99.0) in subjects 50 years and older (Table 2).

Table 2. Efficacy of SHINGRIX on Incidence of Herpes Zoster Compared with Placebo in Study 1^a (mTVC^b)

Age Group	SHINGRIX		Placebo		% Efficacy (95% CI)
		Incidence Rate of HZ per 1,000 Person-		Incidence Rate of HZ per 1,000 Person-	

(Years)	N	n	Years	N	n	Years	
Overall (≥50) ^c	7,344	6	0.3	7,415	210	9.1	97.2 (93.7, 99.0)
50 - 59	3,492	3	0.3	3,525	87	7.8	96.6 (89.6, 99.3)
60 - 69	2,141	2	0.3	2,166	75	10.8	97.4 (90.1, 99.7)
≥70	1,711	1	0.2	1,724	48	9.4	97.9 (87.9, 100.0)

N = Number of subjects included in each group; n = Number of subjects having at least 1 confirmed HZ episode; HZ = Herpes zoster; CI = Confidence Interval.

^a Study 1: NCT01165177.

^b mTVC = Modified Total Vaccinated Cohort defined as subjects who received 2 doses (0 and 2 months) of either SHINGRIX or placebo and did not develop a confirmed case of HZ within 1 month after the second dose.

^c Primary study endpoint was based on confirmed HZ cases in subjects aged 50 years and older.

In a descriptive analysis, vaccine efficacy against HZ in subjects aged 50 years and older was 93.1% (95% CI: 81.3, 98.2) in the fourth year post-vaccination.

Occurrence of PHN

Among all subjects aged 50 years or older in the mTVC, no cases of PHN were reported in the vaccine group compared with 18 cases reported in the placebo group.

14.2 Efficacy in Subjects 70 Years and Older

Study 2 was a randomized, placebo-controlled, observer-blind clinical study conducted in 18 countries. Randomization was stratified (3:1) by age: 70 to 79 years and ≥80 years. With the exception of age, the study exclusion criteria were the same as for Study 1. Subjects were followed for the development of HZ and PHN for a median of 3.9 years (range: 0 to 4.5 years). Suspected HZ cases were followed prospectively for the development of PHN as for Study 1.

The primary efficacy analysis population (mTVC) included 13,163 subjects aged 70 years and older who received 2 doses (0 and 2 months) of either SHINGRIX (n = 6,541) or placebo (n = 6,622) and did not develop a confirmed case of HZ within 1 month after the second dose. In the mTVC population, 54.7% were female; 77.6% were white, 17.1% were Asian, 1.0% were black, and 4.2% were of other racial/ethnic groups. The mean age of subjects was 75.5 years.

Confirmed HZ cases were determined by either PCR (92.3%) or by a Clinical Evaluation Committee (7.7%).

Efficacy against Herpes Zoster

Vaccine efficacy results against HZ in subjects 70 years and older are shown in Table 3.

Table 3. Efficacy of SHINGRIX on Incidence of Herpes Zoster Compared with Placebo in Study 2^a (mTVC^b)

Age Group (Years)	SHINGRIX			Placebo			% Efficacy (95% CI)
	N	n	Incidence Rate of HZ per 1,000 Person-Years	N	n	Incidence Rate of HZ per 1,000 Person-Years	
Overall (≥70) ^c	6,541	23	0.9	6,622	223	9.2	89.8 (84.3, 93.7)
70 - 79	5,114	17	0.9	5,189	169	8.8	90.0 (83.5, 94.3)
≥80	1,427	6	1.2	1,433	54	11.0	89.1 (74.7, 96.2)

N = Number of subjects included in each group; n = Number of subjects having at least 1 confirmed HZ episode; HZ = Herpes zoster; CI = Confidence Interval.

^a Study 2: NCT01165229.

^b mTVC = Modified Total Vaccinated Cohort defined as subjects who received 2 doses (0 and 2 months) of either SHINGRIX or placebo and did not develop a confirmed case of HZ within 1 month after the second dose.

^c Primary study endpoint was based on confirmed HZ cases in subjects aged 70 years and older.

In a descriptive analysis, vaccine efficacy against HZ in subjects 70 years and older was 85.1% (95% CI: 64.5, 94.8) in the fourth year after vaccination.

Efficacy against PHN

Among all subjects aged 70 years or older in the mTVC, 4 cases of PHN were reported in the vaccine group, compared with 28 cases reported in the placebo group. Vaccine efficacy against PHN was 85.5% (95% CI: [58.5; 96.3]). The benefit of SHINGRIX in the prevention of PHN can be attributed to the effect of the vaccine on the prevention of HZ.

Reduction of Use of Pain Medication

Among subjects with confirmed HZ, the use of HZ-associated pain medications was reported for 10 of 23 subjects (43.5%) who received SHINGRIX and for 160 of 223 subjects (71.7%) who received placebo.

14.3 Pooled Efficacy Analyses across Studies 1 and 2

The efficacy of SHINGRIX to prevent HZ and PHN in subjects 70 years and older was evaluated by combining the results from Studies 1 and 2 through a pre-specified pooled analysis in the mTVC. A total of 8,250 and 8,346 subjects who received SHINGRIX and placebo, respectively, were included in the pooled mTVC analysis.

Efficacy against Herpes Zoster

Compared with placebo, SHINGRIX significantly reduced the risk of developing HZ by 91.3% (95% CI: 86.9, 94.5) in subjects 70 years and older (Table 4).

Table 4. Efficacy of SHINGRIX on Incidence of Herpes Zoster Compared with Placebo in Studies 1 and 2 (Pooled Data^a) (mTVC^b)

Age Group (Years)	SHINGRIX			Placebo			% Efficacy (95% CI)
	N	n	Incidence Rate of HZ per 1,000 Person-Years	N	n	Incidence Rate of HZ per 1,000 Person-Years	
Overall (≥70) ^c	8,250	25	0.8	8,346	284	9.3	91.3 (86.9, 94.5)
70 - 79	6,468	19	0.8	6,554	216	8.9	91.3 (86.0, 94.9)
≥80	1,782	6	1.0	1,792	68	11.1	91.4 (80.2, 96.9)

N = Number of subjects included in each group; n = Number of subjects having at least 1 confirmed HZ episode; HZ = Herpes zoster; CI = Confidence Interval.

^a Pooled data from Study 1: NCT01165177 (subjects ≥50 years) and Study 2: NCT01165229 (subjects ≥70 years).

^b mTVC = Modified Total Vaccinated Cohort defined as subjects who received 2 doses (0 and 2 months) of either SHINGRIX or placebo and did not develop a confirmed case of HZ within 1 month after the second dose.

^c Primary endpoint of pooled analysis was based on confirmed HZ cases in subjects 70 years and older.

Efficacy against PHN

Table 5 compares the overall rates of PHN in the vaccine and placebo groups across both studies.

Table 5. Efficacy of SHINGRIX on Overall Incidence of Postherpetic Neuralgia Compared with Placebo in Studies 1 and 2 (Pooled Data^a) (mTVC^b)

Age Group (Years)	SHINGRIX			Placebo			% Efficacy (95% CI)
	N	n	Incidence Rate of PHN ^c per 1,000 Person-Years	N	n	Incidence Rate of PHN per 1,000 Person-Years	
Overall (≥70)	8,250	4	0.1	8,346	36	1.2	88.8 (68.7, 97.1)
70 - 79	6,468	2	0.1	6,554	29	1.2	93.0 (72.5, 99.2)
≥80	1,782	2	0.3	1,792	7	1.1	71.2 (-51.5, 97.1)

N = Number of subjects included in each group; n = Number of subjects having at least 1 PHN; CI = Confidence Interval.

^a Pooled data from Study 1: NCT01165177 (subjects ≥50 years) and Study 2: NCT01165229 (subjects ≥70 years).

^b mTVC = Modified Total Vaccinated Cohort defined as subjects who received 2 doses (0 and 2 months) of either SHINGRIX or placebo and did not develop a confirmed case of HZ within 1 month after the second dose.

^c PHN = Postherpetic neuralgia defined as HZ-associated pain rated as 3 or greater (on a 0- to 10 point scale) occurring or persisting at least 90 days following the onset of rash using Zoster Brief Pain Inventory questionnaire.

The benefit of SHINGRIX in the prevention of PHN can be attributed to the effect of the vaccine on the prevention of HZ. The efficacy of SHINGRIX in the prevention of PHN in subjects with confirmed HZ could not be demonstrated.

14.4 Immunological Evaluation to Support Dosing Schedule

A measure of the immune response that confers protection against HZ is unknown. Anti-gE antibody levels were measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA) and were used to support the dosing schedule.

In an open-label clinical study, 238 subjects 50 years and older received SHINGRIX on either a 0- and 2-month or 0- and 6-month schedule. Non-inferiority of the 0- and 6-month schedule compared with the 0- and 2-month schedule based on anti-gE ELISA GMCs 1 month after the second dose was demonstrated.

14.5 Concomitant Administration with Influenza Vaccine

In an open-label clinical study, subjects 50 years and older received 1 dose each of SHINGRIX and FLUARIX QUADRIVALENT (QIV) at Month 0 and 1 dose of SHINGRIX at

Month 2 (n = 413), or 1 dose of QIV at Month 0 and 1 dose of SHINGRIX at Months 2 and 4 (n = 415). There was no evidence for interference in the immune response to any of the antigens contained in SHINGRIX or the coadministered vaccine.

16 HOW SUPPLIED/STORAGE AND HANDLING

SHINGRIX is supplied as 2 components: A single-dose vial of lyophilized gE antigen component (powder) and a single-dose vial of adjuvant suspension component (liquid) (packaged without syringes or needles).

Table 6: Product Presentations for SHINGRIX

Presentation	Carton NDC Number	Components	
		Adjuvant Suspension Component (liquid)	Lyophilized gE Antigen Component (powder)
An outer carton of 1 dose	58160-819-12	Vial 1 of 2 NDC 58160-829-01	Vial 2 of 2 NDC 58160-828-01
An outer carton of 10 doses	58160-823-11	10 vials NDC 58160-829-03	10 vials NDC 58160-828-03

16.1 Storage before Reconstitution

Adjuvant suspension component vials: Store refrigerated between 2° and 8°C (36° and 46°F). Protect vials from light. Do not freeze. Discard if the adjuvant suspension has been frozen.

Lyophilized gE antigen component vials: Store refrigerated between 2° and 8°C (36° and 46°F). Protect vials from light. Do not freeze. Discard if the antigen component has been frozen.

16.2 Storage after Reconstitution

- Administer immediately or store refrigerated between 2° and 8°C (36° and 46°F) for up to 6 hours prior to use.
- Discard reconstituted vaccine if not used within 6 hours.
- Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

- Inform patients of the potential benefits and risks of immunization with SHINGRIX and of the importance of completing the 2-dose immunization series according to the schedule.
- Inform patients about the potential for adverse reactions that have been temporally associated with administration of SHINGRIX.
- Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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Research Triangle Park, NC 27709

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SHX:5PI

gE Recombinant Varicella Zoster Virus (VZV) glycoprotein E



SHINGRIX

zoster vaccine recombinant, adjuvanted kit

Product Information

Product Type	VACCINE	Item Code (Source)	NDC:50090-3372(NDC:58160-823)
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50090-3372-0	1 in 1 KIT; Type 0: Not a Combination Product		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	20 VIAL	10 mL
Part 2	20 VIAL	10 mL

Part 1 of 2

SHINGRIX

ge recombinant varicella zoster virus (vzv) glycoprotein e injection, powder, lyophilized, for suspension

Product Information

Item Code (Source)	NDC:58160-828
Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RECOMBINANT VARICELLA ZOSTER VIRUS GLYCOPROTEIN E ANTIGEN (UNII: COB9FF6I46) (RECOMBINANT VARICELLA ZOSTER VIRUS GLYCOPROTEIN E ANTIGEN - UNII:COB9FF6I46)	RECOMBINANT VARICELLA ZOSTER VIRUS GLYCOPROTEIN E ANTIGEN	50 ug in 0.5 mL

Inactive Ingredients

Ingredient Name	Strength
SUCROSE (UNII: C151H8M554)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SODIUM PHOSPHATE, MONOBASIC, DIHYDRATE (UNII: 5QWK665956)	
DIBASIC POTASSIUM PHOSPHATE (UNII: CI71S98N1Z)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:58160-828-03	0.5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125614	10/20/2017	

Part 2 of 2

AS01B

as01b suspension

Product Information

Item Code (Source)	NDC:58160-829
Route of Administration	INTRAMUSCULAR

Inactive Ingredients

Ingredient Name	Strength
MONOPHOSPHORYL LIPID A (UNII: MWC0ET1L2P)	
QS-21 (UNII: 61H83WZX3U)	
DIOLEOYLPHOSPHATIDYLCHOLINE, DL- (UNII: EDS2L3ODLV)	
CHOLESTEROL (UNII: 97C5T2UQ7J)	
POTASSIUM PHOSPHATE, MONOBASIC (UNII: 4J9FJ0HL51)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:58160-829-03	0.5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125614	10/20/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125614	10/20/2017	

Labeler - A-S Medication Solutions (830016429)

Establishment

Name	Address	ID/FEI	Business Operations
A-S Medication Solutions		830016429	RELABEL(50090-3372)