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House Bill 1468
Human Services Committee
January 25, 2021, 2 p.m.

Good afternoon, Chairman Weisz and members of the Human Services Committee. My name is Molly Howell, and I am the Immunization Director at the North Dakota Department of Health (NDDoH). I am providing testimony in opposition to HB1468.

The NDDoH agrees that there should be informed consent for vaccination. In fact, there already is informed consent. Before each dose that is administered to children, health care providers are required by federal law to provide a vaccine information statement (VIS). Because COVID-19 vaccination is under emergency use authorization (EUA), an EUA fact sheet is required. The VIS and EUA factsheets provide information in plain language about the risks and benefits of vaccination. These factsheets inform the public about how to report vaccine adverse events. They explain who should and should not be vaccinated. VISs are approved by the Advisory Committee on Childhood Vaccines, which includes three members of the public (two of which are parents of vaccine-injured children) and three attorneys. Package inserts, on the other hand, are written in scientific language and intended for health care providers. They include information from clinical trials, even if unrelated to vaccination. For example, if a trial participant gets into a car accident and dies.

The NDDoH Division of Immunization conducts site visits at health care provider offices and assesses whether health care providers have up-to-date VISs on hand and that providers are routinely offering them. Each Vaccines For Children (VFC) Program enrolled provider site (195) receives at least one site visit every other year.

In 2020, 689,890 vaccine doses were administered in North Dakota according to the North Dakota Immunization Information System (NDIIS). If a package insert needs to be provided, in addition to a VIS, with each dose that will cost health care providers an estimated $1 per dose for about **$1.38 million** for the biennium. This is likely a low-cost estimate with a higher number of doses administered anticipated due to COVID-19 vaccination. This estimate is based on a package insert length of 10 pages and $0.10 per page, double-sided and stapled. Some package inserts are as long as 43 pages.

I have attached an example of a VIS and an example of a package insert. Also attached is an informative fact sheet from Vaccinate Your Family that explains what a VIS is and why it is used instead of a package insert.

Exemption information for child care and school immunizations is already available on our website. Exemption information is available on the exact same document as information about requirements. The Certificate of Immunization also includes exemption information and is available on our website.

Pregnant women are recommended to be vaccinated against influenza and pertussis. A 2018 study showed that getting a flu shot reduced a pregnant woman's risk of being hospitalized with flu by an average of 40%. Pregnant women who get a flu vaccine also are helping to protect their babies from flu illness for the first several months after their birth, when they are too young to get vaccinated. Protection against pertussis (whooping cough) is included in the tetanus, diphtheria, and acellular pertussis vaccine (Tdap). Getting a Tdap vaccine between 27 through 36 weeks of pregnancy lowers the risk of whooping cough in babies younger than 2 months old by 78%. They also receive a VIS informing them of the risks and benefits. There are numerous studies for both Tdap and influenza vaccines that show the safety and benefits of vaccination for pregnant women. The requirement for a "witness" to be present when vaccinating a pregnant woman creates an additional burden for already limited health care providers in North Dakota.

For the reasons I have outlined today, the NDDoH asks you to oppose HB1468. This concludes my testimony. I am happy to answer any questions you may have.

Vaccine Information Statements (VISs) Provide Informed Consent on Vaccines

For meaningful informed consent about vaccinations, you need materials that:

- Are accurate
- Cover necessary information in a way that is understandable to most people
- Link to more detailed information for those who want it

Vaccine Information Statements (VIS) provide informed consent about the risks and benefits of vaccinations. Materials that are too technical, lengthy, unclear or provide confusing information can undermine informed consent.

What is a VIS?

- VISs are important sources of vaccine information for the public. They are written in easy-to-understand language to help vaccine-recipients (or their parents/caregivers) better understand the risks and benefits of vaccines.
- Each VIS includes the benefits and risks of each vaccine, and clearly outlines the process for reporting to the Vaccine Adverse Event Reporting System (VAERS) as well as filing a claim with the National Vaccine Injury Compensation Program (VICP), if necessary.
- Federal law requires that a VIS be provided to patients or parents/caregivers *before* each and every vaccine is administered. It must be given regardless of the age of the vaccine recipient.
- Healthcare providers must also record specific information in the patient's medical record or permanent office log, including the edition date of the VIS, the date the VIS was given, the vaccine administration date, the office address and name and title of the person who administers the vaccine, and the vaccine manufacturer and lot number.

Who writes a VIS?

- Each VIS is written by the Centers for Disease Control and Prevention (CDC), and the content is informed by a group of independent experts and parents, including representatives from Vaccinate Your Family and the National Vaccine Information Center – two organizations with divergent views of vaccinations.
- The wording of each VIS is carefully crafted to ensure that it adheres to the health literacy criteria set forth in the health literacy standards of *The Patient Protection and Affordable Care Act of 2010*.
- Each VIS is reviewed and approved by the Advisory Committee on Childhood Vaccines (ACCV), which includes:
    - Three members of the general public, including at least two who are the parents or guardians of children who have suffered a vaccine-related injury.

- Three members who are attorneys, including at least one who represents individuals who may have been vaccine-injured.

Why are VISs given to patients instead of the vaccine package insert?

- Vaccine manufacturers are required by the FDA to report all events during a clinical trial. For example, if a child is involved in a car accident during the clinical trial and reports to the hospital with a broken arm, the manufacturer must report a broken arm as an adverse event of the vaccine even though we know they are not related.
- Sometimes, a VIS does not exactly match a manufacturer's product insert. That's because VISs follow the Advisory Committee for Immunization Practices' (ACIP's) recommendations. ACIP carefully considers whether adverse events reported during clinical trials could be causally linked to the vaccination.
- ACIP has the ability to remove non-related injuries for the sake of clarity on a VIS. However, it is important to note that the final section of each VIS - *How can I learn more?* - states that parents and patients can ask their healthcare providers for the package insert.

Where can I find more information about Vaccine Information Statements?

- The CDC has all of the English-language VISs on their website: www.cdc.gov/vaccines/hcp/vis/index.html
- The CDC has a page on Frequently-Asked Questions on VISs: www.cdc.gov/vaccines/hcp/vis/about/vis-faqs.html
- VISs have been translated into about 40 languages. These can be found on the Immunization Action Coalition's website: www.immunize.org/vis/

Vaccine Information Statements ensure patients and parents have enough information to make a truly informed decision whether to vaccinate themselves or their children.

Source

National Center for Immunization and Respiratory Diseases. "Vaccine Information Statements (VISs)." *Centers for Disease Control and Prevention.* www.cdc.gov/vaccines/hcp/vis/index.html. Last Accessed: October 3, 2018.

Recombinant Zoster (Shingles) Vaccine: *What You Need to Know*

Many Vaccine Information Statements are available in Spanish and other languages. See www.immunize.org/vis

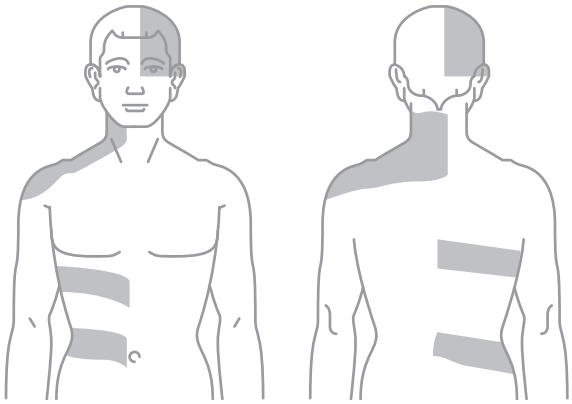
Hojas de información sobre vacunas están disponibles en español y en muchos otros idiomas. Visite www.immunize.org/vis

1 Why get vaccinated?

Recombinant zoster (shingles) vaccine can prevent **shingles**.

Shingles (also called herpes zoster, or just zoster) is a painful skin rash, usually with blisters. In addition to the rash, shingles can cause fever, headache, chills, or upset stomach. More rarely, shingles can lead to pneumonia, hearing problems, blindness, brain inflammation (encephalitis), or death.

The most common complication of shingles is long-term nerve pain called postherpetic neuralgia (PHN). PHN occurs in the areas where the shingles rash was, even after the rash clears up. It can last for months or years after the rash goes away. The pain from PHN can be severe and debilitating.



About 10 to 18% of people who get shingles will experience PHN. The risk of PHN increases with age. An older adult with shingles is more likely to develop PHN and have longer lasting and more severe pain than a younger person with shingles.

Shingles is caused by the varicella zoster virus, the same virus that causes chickenpox. After you have chickenpox, the virus stays in your body and can cause shingles later in life. Shingles cannot be passed from one person to another, but the virus that causes shingles can spread and cause chickenpox in someone who had never had chickenpox or received chickenpox vaccine.

2 Recombinant shingles vaccine

Recombinant shingles vaccine provides strong protection against shingles. By preventing shingles, recombinant shingles vaccine also protects against PHN.

Recombinant shingles vaccine is the preferred vaccine for the prevention of shingles. However, a different vaccine, live shingles vaccine, may be used in some circumstances.

The recombinant shingles vaccine is recommended for **adults 50 years and older** without serious immune problems. It is given as a two-dose series.

This vaccine is also recommended for people who have already gotten another type of shingles vaccine, the live shingles vaccine. There is no live virus in this vaccine.

Shingles vaccine may be given at the same time as other vaccines.

3 Talk with your health care provider

Tell your vaccine provider if the person getting the vaccine:

- Has had an **allergic reaction after a previous dose of recombinant shingles vaccine**, or has any **severe, life-threatening allergies**.
- Is **pregnant or breastfeeding**.
- Is **currently experiencing an episode of shingles**.

In some cases, your health care provider may decide to postpone shingles vaccination to a future visit.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

People with minor illnesses, such as a cold, may be vaccinated. People who are moderately or severely ill should usually wait until they recover before getting recombinant shingles vaccine.

Your health care provider can give you more information.

4 Risks of a vaccine reaction

- A sore arm with mild or moderate pain is very common after recombinant shingles vaccine, affecting about 80% of vaccinated people. Redness and swelling can also happen at the site of the injection.
- Tiredness, muscle pain, headache, shivering, fever, stomach pain, and nausea happen after vaccination in more than half of people who receive recombinant shingles vaccine.

In clinical trials, about 1 out of 6 people who got recombinant zoster vaccine experienced side effects that prevented them from doing regular activities. Symptoms usually went away on their own in 2 to 3 days.

You should still get the second dose of recombinant zoster vaccine even if you had one of these reactions after the first dose.

People sometimes faint after medical procedures, including vaccination. Tell your provider if you feel dizzy or have vision changes or ringing in the ears.

As with any medicine, there is a very remote chance of a vaccine causing a severe allergic reaction, other serious injury, or death.

5 What if there is a serious problem?

An allergic reaction could occur after the vaccinated person leaves the clinic. If you see signs of a severe allergic reaction (hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, or weakness), call **9-1-1** and get the person to the nearest hospital.

For other signs that concern you, call your health care provider.

Adverse reactions should be reported to the Vaccine Adverse Event Reporting System (VAERS). Your health care provider will usually file this report, or you can do it yourself. Visit the VAERS website at **www.vaers.hhs.gov** or call **1-800-822-7967**. *VAERS is only for reporting reactions, and VAERS staff do not give medical advice.*

6 How can I learn more?

- Ask your health care provider.
- Call your local or state health department.
- Contact the Centers for Disease Control and Prevention (CDC):
  - Call **1-800-232-4636** (**1-800-CDC-INFO**) or
  - Visit CDC's website at **www.cdc.gov/vaccines**

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

---------- 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)

---------- 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: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

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.

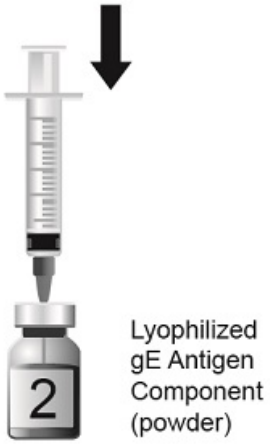


Figure 2. Slowly transfer entire contents of syringe into the lyophilized gE antigen component vial (powder). Vial 2 of 2.

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

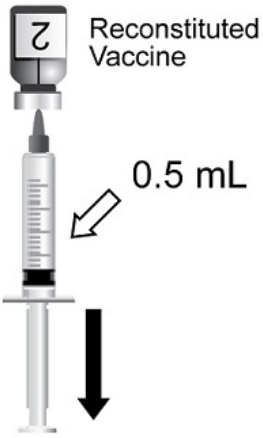


Figure 4. After reconstitution, withdraw 0.5 mL from the vial containing the reconstituted vaccine and administer **intramuscularly**.

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.

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 ≥37.5°C/99.5°F for oral, axillary, or tympanic route, or ≥38°C/100.4°F for rectal route; Grade 3 fever defined as >39.0°C/102.2°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 ≥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.

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 (≤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 (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 (≥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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