Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
These highlights do not include all the information needed to use Flublok® safely and effectively. See full prescribing information for Flublok.

**Flublok (Influenza Vaccine)**
**Injection for Intramuscular Use**
**2024-2025 Formula**
**Initial U.S. Approval: 2013**

**----------INDICATIONS AND USAGE----------**
Flublok is a vaccine indicated for active immunization for the prevention of disease caused by influenza A virus subtypes and influenza type B virus represented by antigens contained in the vaccine. Flublok is approved for use in persons 18 years of age and older. (1)

**---------DOSAGE AND ADMINISTRATION--------**
**For intramuscular use (0.5 mL).** (2)

**-------DOSAGE FORMS AND STRENGTHS--------**
Flublok is an injection, a single dose is 0.5mL. (3)

**----------CONTRAINDICATIONS----------**
- Do not administer Flublok to anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine. (4, 6.2, 11)

**----------WARNINGS AND PRECAUTIONS---------**
- Appropriate medical treatment must be immediately available to manage potential anaphylactic reactions following administration of Flublok. (5.1)
- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of potential benefits and risks. (5.2)

**----------ADVERSE REACTIONS----------**
- In adults 18 through 49 years of age, the most common (≥10%) injection-site adverse reaction was pain (37%); the most common (≥10%) solicited systemic adverse reactions were headache (15%), fatigue (15%) and muscle pain (11%). (6.1)
- In adults 50 through 64 years of age, the most common (≥10%) injection site adverse reaction was pain (32%); the most common (≥10%) solicited systemic adverse reactions were headache (17%), fatigue (13%), and muscle pain (11%). (6.1)
- In adults 65 years of age and older, the most common (≥10%) injection site adverse reaction was pain (19%); the most common (≥10%) solicited systemic adverse reactions were fatigue (13%) and headache (10%). (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., at (1-800-822-2463 (1-800-Vaccine) or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.**

**See 17 for PATIENT COUNSELING INFORMATION.**

Revised: 10/2024

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**FULL PRESCRIBING INFORMATION**

## 1 INDICATIONS AND USAGE

Flublok is a vaccine indicated for active immunization for the prevention of disease caused by influenza A virus subtypes and influenza type B virus represented by antigens contained in the vaccine. Flublok is approved for use in persons 18 years of age and older.

## 2 DOSAGE AND ADMINISTRATION

**For intramuscular use.**

### 2.1 Dosage

Administer Flublok as a single 0.5 mL dose.

### 2.2 Administration

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.

Gently invert the prefilled syringe prior to affixing a sterile needle.

Administer the dose intramuscularly.

## 3 DOSAGE FORMS AND STRENGTHS

Flublok is an injection. A single dose is 0.5 mL.

## 4 CONTRAINDICATIONS

Do not administer Flublok to anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine. *[*see *Postmarketing Experience [6.2] and Description (11)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Managing Allergic Reactions

Appropriate medical treatment must be immediately available to manage potential anaphylactic reactions following administration of Flublok.

### 5.2 Guillain-Barré Syndrome

If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of the potential benefits and risks.

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré Syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than one additional case per 1 million persons vaccinated.

### 5.3 Altered Immunocompetence

If Flublok is administered to immunocompromised individuals, including persons receiving immunosuppressive therapy, the immune response may be diminished.

### 5.4 Limitations of Vaccine Effectiveness

Vaccination with Flublok may not protect all vaccine recipients.

### 5.5 Syncope

Syncope (fainting) has been reported following vaccination with Flublok. Procedures should be in place to avoid injury from fainting.

## 6 ADVERSE REACTIONS

In adults 18 through 49 years of age, the most common (≥10%) injection-site adverse reaction was pain (37%); the most common (≥10%) solicited systemic adverse reactions were headache (15%), fatigue (15%) and muscle pain (11%). (6.1)

In adults 50 through 64 years of age, the most common (≥10%) injection site adverse reaction was pain (32%); the most common (≥10%) solicited systemic adverse reactions were headache (17%), fatigue (13%), and muscle pain (11%). (6.1)

In adults 65 years of age and older, the most common (≥10%) injection site adverse reaction was pain (19%); the most common (≥10%) solicited systemic adverse reactions were fatigue (13%) and headache (10%). (6.1)

### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a vaccine cannot be directly compared to rates in the clinical studies of another vaccine and may not reflect the rates observed in clinical practice.

The safety experience with Flublok Quadrivalent is relevant to Flublok because both vaccines are manufactured using the same process and have overlapping compositions.

Flublok

Flublok has been administered to and safety data collected from 2497 adults 18 through 49 years of age, 972 adults 50 through 64 years of age, and 1078 adults aged 65 years and older enrolled in five randomized, placebo- or active-controlled clinical trials. Clinical safety data for Flublok are presented from four clinical trials (Studies 1, 2, 3, and 4). Data from a placebo-controlled trial in adults 18 through 49 years of age (Study 1) are presented, followed by data pooled according to age group from Studies 2 and 4 (adults 50 through 64 years of age) and Studies 3 and 4 (adults aged 65 years and older).

Reactogenicity data from a small Phase 2 trial (Study 5) in adults 18 through 49 years of age, 153 of whom received Flublok 135mcg, are not presented. However, subjects from Study 5 are included in the description of deaths and serious adverse events (SAEs). In all studies local (injection site) and systemic adverse reactions were solicited with the use of a memory aid for 7 days following vaccination, and unsolicited adverse reactions were collected for 28-30 days post-vaccination. In Studies 1- 3 and 5, SAEs were collected for 6 months post-vaccination via clinic visit or telephone follow up on Day 28, telephone follow up on Day 180, or by spontaneous reporting. Study 4 collected SAEs through 30 days following receipt of vaccine. Study 4 also actively solicited pre-specified common hypersensitivity-type reactions through 30 days following receipt of vaccine as a primary endpoint.

Study 1 (NCT00539981) included 4648 subjects 18 through 49 years of age for safety analysis, randomized to receive Flublok (n=2344) or placebo (n=2304) (see *Clinical Studies [14.1]*).

Study 2 (NCT00539864) included 602 subjects 50 through 64 years of age for safety analysis, randomized to receive Flublok (n=300) or another U.S.-licensed trivalent influenza vaccine (Fluzone, manufactured by Sanofi Pasteur, Inc.) as an active control (n=302).

Study 3 (NCT00395174) included 869 subjects aged 65 years and older for safety analysis, randomized to receive Flublok (n=436) or another U.S.-licensed trivalent influenza vaccine (Fluzone) as an active control (n=433).

Study 4 (NCT01825200) included 2627 subjects aged 50 years and older for safety analysis, randomized to receive Flublok (n=1314) or another U.S.-licensed trivalent influenza vaccine (Afluria, manufactured by bioCSL Pty Ltd.) as an active control (n=1313). Among subjects 50 through 64 years of age, 672 received Flublok and 665 received Afluria. Among subjects aged 65 years and older, 642 received Flublok and 648 received Afluria.

In a clinical trial of adults 18-49 years of age (Study 1, Table 1) the mean age of participants was 32.5 years, 59% were female, and 67% were Caucasian (see *Clinical Studies [14.1]*).

**Table 1: Frequency of Solicited Local Injection Site Adverse Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok or Placebo in Adults 18-49 Years of Age, Study 1, Total Vaccinated Cohort**[*,†,‡]

| | **Flublok N=2272** | | | **Placebo N=2231** | | |
|---|---|---|---|---|---|---|
| **Local** | **%** | | | **%** | | |
| | Any | Mod[§] | Sev[§] | Any | Mod[§] | Sev[§] |
| Pain | 37 | 2 | <1 | 8 | <1 | <1 |
| Redness | 4 | <1 | <1 | 2 | <1 | <1 |
| Swelling | 3 | <1 | <1 | 2 | <1 | <1 |
| Bruising | 3 | <1 | <1 | 3 | <1 | <1 |
| **Systemic** | **%** | | | **%** | | |
| Headache | 15 | 3 | <1 | 16 | 3 | <1 |
| Fatigue | 15 | 3 | <1 | 14 | 3 | <1 |
| Muscle Pain | 11 | 2 | <1 | 7 | <1 | <1 |
| Nausea | 6 | 1 | <1 | 5 | 1 | <1 |
| Joint pain | 4 | <1 | <1 | 4 | <1 | <1 |
| Chills | 3 | <1 | <1 | 3 | <1 | <1 |
| Fever[¶] | <1 | <1 | <1 | <1 | <1 | <1 |

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.

[*] Total Vaccinated Cohort is defined as all randomized subjects who received study vaccine according to the treatment actually received and who provided data.

[†] Study 1 is registered as NCT00539981 under the National Clinical Trials registry.

[‡]Denominators for Study 1: The total number of enrolled, randomized, and vaccinated subjects was 2344 in the Flublok group and 2304 in the placebo group. For all categories except fever, the number of subjects with missing values was 72 in the Flublok group and 73 in the Placebo group so that these denominators are 2272 and 2231 respectively. For fever, 89 Flublok recipients and 104 Placebo recipients were missing data, making these denominators 2255 and 2200 respectively.

[§]Moderate = had it, and it was bad enough to prevent a significant part of usual activities; Severe = had it, and it prevented most or all of normal activities, or had to see a doctor for prescription medicine.

[¶]Fever defined as ≥100.4°F (38°C). Mild (≥100.4º to <101.1ºF); Moderate (≥101.2ºF to <102.2ºF); Severe (≥102.2ºF)

Across three clinical trials (Studies 2 – 4, Tables 2 and 3) a total of 2050 adults age 50 years and older received Flublok and 2048 received a U.S.-licensed trivalent inactivated influenza vaccine (IIV3) comparator. The mean age of Flublok study participants was 65 years; 56% were female and 80% were Caucasian.

The incidence of solicited reactogenicity differed between adults 50 through 64 years of age and adults aged 65 years and older. Therefore, data from Studies 2, 3, and 4 were pooled according to age group and are presented separately (Tables 2 and 3).

Most adverse reactions in both age groups were mild in severity.

**Table 2: Frequency of Solicited Local Injection Site Adverse Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok or Comparator in Adults 50-64 Years of Age, Studies 2 and 4, Total Vaccinated Cohort*,†**

| | Flublok N=972 | | | IIV3† N=967 | | |
|---|---|---|---|---|---|---|
| | **Any** | **Mod‡** | **Sev‡** | **Any** | **Mod‡** | **Sev‡** |
| **Local** | **%** | | | | | |
| Pain | 32 | 2 | <1 | 37 | <1 | 0 |
| Firmness/Swelling | 7 | 2 | <1 | 6 | 1 | <1 |
| Redness | 6 | 2 | <1 | 5 | 1 | <1 |
| | | | | | | |
| **Systemic** | **%** | | | | | |
| Headache | 17 | 4 | <1 | 16 | 3 | <1 |
| Fatigue | 13 | 3 | <1 | 17 | 3 | <1 |
| Muscle Pain | 11 | 2 | <1 | 11 | 2 | <1 |
| Joint Pain | 8 | 2 | <1 | 8 | 2 | <1 |
| Nausea | 6 | 1 | 0 | 5 | <1 | <1 |
| Shivers/Chills | 5 | 1 | 0 | 4 | <1 | <1 |
| Fever§ | <1 | <1 | <1 | <1 | 0 | 0 |

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.

*Total Vaccinated Cohort is defined as all randomized subjects who received study vaccine according to the treatment actually received and who provided data.

† Pooled Data from Studies 2 and 4. For Studies 2 and 4, the U.S.-licensed IIV3 comparators were Fluzone and Afluria, respectively. Studies 2 and 4 are registered as NCT00539864 and NCT01825200, respectively, under the National Clinical Trials registry.

‡ Moderate = had it, and it was bad enough to prevent a significant part of usual activities; Severe = had it, and it prevented most or all of normal activities, or had to see a doctor for prescription medicine.

§Fever defined as ≥100.4°F (38°C). Mild (≥100.4º to <101.1ºF); Moderate (≥101.2ºF to <102.2ºF); Severe (≥102.2ºF) For fever, 12 Flublok recipients and 5 IIV3 recipients were missing data, making these denominators 964 and 962, respectively.

**Table 3: Frequency of Solicited Local Injection Site Adverse Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok or Comparator in Adults ≥65 Years of Age, Studies 3 and 4, Total Vaccinated Cohort** [*,†]

| | Flublok N=1078 | | | IIV3[†] N=1081 | | |
|---|---|---|---|---|---|---|
| | Any | Mod[‡] | Sev[‡] | Any | Mod[‡] | Sev[‡] |
| **Local** | % | | | | | |
| Pain | 19 | <1 | <1 | 20 | <1 | <1 |
| Redness | 7 | 1 | <1 | 7 | 1 | 1 |
| Firmness/Swelling | 7 | 2 | <1 | 7 | <1 | <1 |
| **Systemic** | % | | | | | |
| Fatigue | 13 | 3 | <1 | 15 | 2 | <1 |
| Headache | 10 | <1 | <1 | 9 | 1 | <1 |
| Muscle Pain | 8 | 2 | <1 | 8 | 1 | <1 |
| Joint Pain | 6 | 1 | <1 | 6 | 1 | <1 |
| Shivers/Chills | 5 | <1 | <1 | 5 | <1 | <1 |
| Nausea | 4 | <1 | <1 | 3 | <1 | <1 |
| Fever[§] | 3 | <1 | <1 | 2 | 0 | 0 |

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.

[*]Total Vaccinated Cohort is defined as all randomized subjects who received study vaccine according to the treatment actually received and who provided data.

[†]Pooled Data from Studies 3 and 4. For Studies 3 and 4, the U.S.-licensed IIV3 comparators were Fluzone and Afluria, respectively. Studies 3 and 4 are registered as NCT00395174 and NCT01825200, respectively, under the National Clinical Trials registry.

[‡]Moderate = had it, and it was bad enough to prevent a significant part of usual activities; Severe = had it, and it prevented most or all of normal activities, or had to see a doctor for prescription medicine.

[§]Fever defined as ≥100.4°F (38°C). Mild (≥100.4º to <101.1ºF); Moderate (≥101.2ºF to <102.2ºF); Severe (≥102.2ºF)

Among adults 18-49 years of age (Studies 1 and 5 pooled), through 6 months post-vaccination, two deaths were reported, one in a Flublok recipient and one in a placebo recipient. Both deaths occurred more than 28 days following vaccination and neither was considered vaccine-related. SAEs were reported by 32 Flublok recipients and 35 placebo recipients. One SAE in a Flublok recipient was assessed as possibly related to the vaccine: pleuropericarditis with effusions requiring hospitalization and drainage. No specific cause was identified. The patient recovered.

Among adults 50-64 years of age (Studies 2 and 4 pooled), through up to 6 months or 30 days, post- vaccination, respectively, there were no deaths; SAEs were reported by 10 subjects, 6 Flublok recipients and 4 IIV3 recipients. One of the SAEs, vasovagal syncope following injection of Flublok, was considered related to administration of study vaccine. Among adults 65 years of age and older (Studies 3 and 4 pooled), through up to 6 months or 30 days post-vaccination, respectively, there were 4 deaths, 2 in Flublok recipients and 2 in IIV3 recipients. None were considered related to the study vaccines. SAEs were reported from 80 subjects, 37 Flublok recipients, 43 in IIV3 recipients. No SAEs were considered related to the study vaccines.

In Study 1 (adults 18-49 years of age), the most frequent unsolicited adverse events, occurring in 1%-2% of subjects, were nasopharyngitis, upper respiratory infection, headache, cough, nasal congestion, pharyngolaryngeal pain, and rhinorrhea.

Among adults 50-64 years of age (Studies 2 and 4 pooled), the most frequent unsolicited adverse events, occurring in 1% of subjects, were diarrhea and cough. Among adults ≥65 years of age (Studies 3 and 4 pooled), the most frequent unsolicited adverse events, occurring in 1% of subjects, were nasopharyngitis and cough.

Among adults 50 years of age and older (Study 4) for whom the incidence of rash, urticaria, swelling, non- pitting edema, or other potential hypersensitivity reactions were actively solicited for 30 days following vaccination, a total of 2.4% of Flublok recipients and 1.6% of IIV3 recipients reported such events over the 30 day follow-up period. A total of 1.9% and 0.9% of Flublok and IIV3 recipients, respectively, reported these events in the 7 days following vaccination. Of these solicited events, rash was most frequently reported (Flublok 1.3%, IIV3 0.8%) over the 30 day follow-up period.

Flublok Quadrivalent

Flublok Quadrivalent has been administered to and safety data collected from 4328 adults 50 years of age and older (Study 6[*]) and 998 adults 18-49 years of age (Study 7[†]).

SAEs were collected for 6 months post-vaccination via clinic visit or remote contact.

Study 6 (NCT02285998) enrolled subjects 50 years of age and older, randomized to receive Flublok Quadrivalent or Comparator (Fluarix Quadrivalent, manufactured by GlaxoSmithKline) as an active control *[see Clinical Studies (14.1)]*. The safety analysis population included 4328 Flublok Quadrivalent recipients and 4344 Comparator vaccine recipients. The mean age of participants was 62.7 years. Overall, 58% of subjects were female, 80% white/Caucasian, 18% black/African American, 0.9% American Indian/Alaskan Native, 0.4% Asian, 0.2% Native Hawaiian/Pacific Islander, 0.7% other racial groups, and 5% of Hispanic/Latino ethnicity.

Among adults 50 years of age and older (Study 6), there were no SAEs considered related to study vaccine.

Study 7 (NCT02290509) enrolled subjects 18 through 49 years of age randomized to receive Flublok Quadrivalent or a Comparator inactivated influenza vaccine (Fluarix® Quadrivalent, manufactured by GlaxoSmithKline). The safety analysis population included 998 recipients of Flublok Quadrivalent and 332 Comparator vaccine recipients. The mean age of participants was 33.5 years. Overall, 65% of subjects were female, 59% white/Caucasian, 37% black/African American, 1.0% Native Hawaiian/Pacific Islander, 0.8% American Indian/Alaskan Native, 0.5% Asian, 1.4% other racial groups, and 16% of Hispanic/Latino ethnicity.

Among adults 18-49 years of age (Study 7), through 6 months post-vaccination, there were no SAEs considered related to study vaccine.

### 6.2 Postmarketing Experience

The following events have been spontaneously reported during post approval use of Flublok or Flublok Quadrivalent. They are described because of the temporal relationship, the biologic plausibility for a causal relationship to Flublok or Flublok Quadrivalent, and their potential seriousness. Because these events 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 vaccine exposure.

Immune system disorders: anaphylaxis, allergic reactions, and other forms of hypersensitivity (including urticaria).

Nervous system disorders: facial palsy (Bell's palsy), Guillain-Barré syndrome, syncope.

[*] NCT02285998
[†] NCT02290509

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Exposure

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Flublok.

Healthcare providers are encouraged to enroll women who receive Flublok during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463 or online by completing data collection form on https://www.sanofipasteurpregnancyregistry.com.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background rates of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Available data from a post-licensure observational, retrospective safety surveillance study showed no evidence of a vaccine-associated increase in the risk of major birth defects and miscarriages when Flublok Quadrivalent is administered during pregnancy (see *Data*). Data for Flublok Quadrivalent are relevant to Flublok because both vaccines are manufactured using the same process and have overlapping compositions.

A developmental study of Flublok has been performed in rats administered 0.5 mL (divided, a single human dose is 0.5 mL) of Flublok prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to Flublok (see *Data*).

Clinical Considerations

*Disease-associated Maternal and/or Embryo/Fetal Risk*

Pregnant women are at increased risk of complications associated with influenza infection compared to non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

*Human*

A post-licensure observational, retrospective safety surveillance study (NCT04460781) included 14,981 pregnant individuals, including those with chronic conditions, who were exposed to Flublok Quadrivalent during the 28 days prior to conception (date of conception defined as the date of the last menstrual period (Day 0) plus 14 days) or during pregnancy. The study was conducted during Northern Hemisphere influenza seasons 2018-2019 and 2019-2020. Pre-specified outcomes included spontaneous abortion and congenital/fetal anomalies. Data were not collected on ectopic pregnancy or elective terminations.

Among 14,981 recipients of Flublok Quadrivalent with known pregnancy outcomes, 750 pregnant individuals received the vaccine during the 28 days prior to conception, 5,092 during the first trimester, 4,851 during the second trimester, and 4,288 during the third trimester. Among 5,842 individuals exposed to Flublok Quadrivalent during the 28 days prior to conception or the first trimester, miscarriage was reported in 464 (3.1%). Among individuals exposed to Flublok Quadrivalent at any time during pregnancy, 1113 pregnancies (7.7%) had infants with major birth defects (56, 360, 381, and 316 among individuals exposed during the 28 days prior to conception, first trimester, second trimester and the third trimester, respectively). The consistency in rate of major birth defects, irrespective of timing of exposure to Flublok Quadrivalent (7.1% [416/5842] among individuals exposed during the 28 days prior to conception and during the first trimester, the period when the risk of major birth defects is highest, and 7.6% [697/9139] among individuals exposed during the second and third trimester) and the lack of pattern of

major birth defects is reassuring.

*Animal*

In a developmental toxicity study, female rats were administered Flublok by intramuscular injection twice prior to mating (35 days and 14 days prior to mating) and on gestation Day 6. The total dose was 0.5 mL (divided) on each occasion (a human dose is 0.5 mL). No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development or female fertility were observed in the study.

### 8.2 Lactation

Risk Summary

It is not known whether Flublok is excreted in human milk. Data are not available to assess the effects of Flublok 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 Flublok and any potential adverse effects on the breastfed child from Flublok or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

### 8.4 Pediatric Use

Data from a randomized, controlled trial demonstrated that children 6 months to less than 3 years of age had diminished hemagglutinin inhibition (HI) responses to Flublok compared to a U.S.-licensed influenza vaccine approved for use in this population, strongly suggesting that Flublok would not be effective in children younger than 3 years of age. Safety and effectiveness of Flublok have not been established in children 3 years to less than 18 years of age.

### 8.5 Geriatric Use

Data from an efficacy study (Study 6), which included 1759 subjects ≥65 years and 525 subjects ≥75 years who received Flublok Quadrivalent, are insufficient to determine whether elderly subjects respond differently from younger subjects (See *Clinical Studies [14]*). Data for Flublok Quadrivalent are relevant to Flublok because both vaccines are manufactured using the same process and have overlapping compositions.

## 11 DESCRIPTION

Flublok [Influenza Vaccine] is a sterile, clear, colorless injection containing recombinant hemagglutinin (HA) proteins from three influenza viruses for intramuscular use. It contains purified HA proteins produced in a continuous insect cell line (*expres*SF+®) that is derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda* (which is related to moths, caterpillars and butterflies), and grown in serum-free medium composed of chemically-defined lipids, vitamins, amino acids, and mineral salts. Each of the three HAs is expressed in this cell line using a baculovirus vector (*Autographa californica* nuclear polyhedrosis virus), extracted from the cells with Triton X-100 and further purified by column chromatography. The purified HAs are then blended and filled into single-dose syringes.

Flublok is standardized according to United States Public Health Service (USPHS) requirements. For the 2024-2025 influenza season it is formulated to contain 135 mcg HA per 0.5 mL dose, with 45 mcg HA of each of the following 3 influenza virus strains: A/West Virginia/30/2022 (A/Wisconsin/67/2022 pdm09-like virus) (H1N1), A/Massachusetts/18/2022 (H3N2) and B/Austria/1359417/2021.

A single 0.5 mL dose of Flublok contains sodium chloride (4.4 mg), monobasic sodium phosphate (0.2 mg), dibasic sodium phosphate (0.5 mg), and polysorbate 20 (Tween®20) (27.5 mcg). Each 0.5 mL dose of Flublok may also contain residual amounts of baculovirus and *Spodoptera frugiperda* cell proteins (≤ 14.3 mcg), baculovirus and cellular DNA (≤ 10 ng), and Triton X-100 (≤ 100 mcg).

Flublok contains no egg proteins, antibiotics, or preservatives. The single-dose, prefilled syringes contain no natural rubber latex.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Flublok contains recombinant HA proteins of the three strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine. These proteins function as antigens which induce a humoral immune response, measured by hemagglutination inhibition (HI) antibody).

Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual replacement of one or more influenza virus strains in each year's influenza vaccine.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Flublok has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals.

## 14 CLINICAL STUDIES

### 14.1 Efficacy Against Laboratory-Confirmed Influenza

The efficacy of Flublok in protecting against culture-confirmed influenza illness was evaluated in a randomized, observer-blind, placebo-controlled multicenter trial conducted in the U.S. during the 2007-2008 influenza season in adults 18-49 years of age (Study 1).

Study 1 enrolled and vaccinated 4648 healthy adults (mean age 32.5 years) randomized in a 1:1 ratio to receive a single dose of Flublok (n=2344) or saline placebo (n=2304). Among enrolled subjects, 59% were female, 67% were white, 19% African-American, 2% Asian, < 1% other races, and 11% of Latino/Hispanic ethnicity. Culture-confirmed influenza was assessed by active and passive surveillance for influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 7 months post- vaccination. ILI was defined as having at least 2 of 3 symptoms (no specified duration) in the following categories: 1) fever ≥ 100ºF; 2) respiratory symptoms (cough, sore throat, or runny nose/stuffy nose); or 3) systemic symptoms (myalgias, arthralgias, headache, chills/sweats, or tiredness/malaise). For subjects with an episode of ILI, nasal and throat swab samples were collected for viral culture.

The primary efficacy endpoint of Study 1 was Centers for Disease Control-defined influenza-like illness (CDC-ILI) with a positive culture for an influenza virus strain antigenically resembling a strain represented in Flublok. CDC-ILI is defined as fever of ≥100°F oral accompanied by cough, sore throat, or both on the same day or on consecutive days. Attack rates and vaccine efficacy (VE), defined as the reduction in the influenza rate for Flublok relative to placebo, were calculated for the total vaccinated cohort (n=4648).

The pre-defined success criterion for the primary efficacy analysis was that the lower bound of the 95% confidence interval (CI) of VE should be at least 40%. Vaccine efficacy against antigenically matched culture-confirmed CDC-ILI could not be determined reliably because 96% of the influenza isolates obtained from subjects in Study 1 were not antigenically matched to the strains represented in the vaccine. An exploratory analysis of VE of Flublok against all strains, regardless of antigenic match, isolated from any subject with an ILI, not necessarily meeting CDC- ILI criteria, demonstrated an efficacy estimate of 44.8% (95% CI 24.4, 60.0). See Table 4 for a presentation of VE by

case definition and antigenic similarity.

**Table 4: Vaccine Efficacy Against Culture-Confirmed Influenza in Healthy Adults 18-49 Years of Age, Study 1***

| Case definition | Flublok (N=2344) | | Saline Placebo (N=2304) | | Flublok Vaccine Efficacy†, % | 95% Confidence Interval |
|---|---|---|---|---|---|---|
| | Cases, n | Rate, % | Cases, n | Rate, % | | |
| Positive culture with a strain represented in the vaccine | | | | | | |
| CDC-ILI, all matched strains‡,§ | 1 | 0.04 | 4 | 0.2 | 75.4 | (-148.0, 99.5) |
| Any ILI, all matched strains¶,# | 2 | 0.1 | 6 | 0.3 | 67.2 | (-83.2, 96.8) |
| Positive culture with any strain, regardless of match to the vaccine | | | | | | |
| CDC-ILI, all strains‡,Þ | 44 | 1.9 | 78 | 3.4 | 44.6 | (18.8, 62.6) |
| Sub-Type A | 26 | 1.1 | 56 | 2.4 | 54.4 | (26.1, 72.5) |
| Type B | 18 | 0.8 | 23 | 1.0 | 23.1 | (-49.0, 60.9) |
| Any ILI, all strains¶ | 64 | 2.7 | 114 | 4.9 | 44.8 | (24.4, 60.0) |
| Sub-Type A | 41 | 1.7 | 79 | 3.4 | 49.0 | (24.7, 65.9) |
| Type B | 23 | 1.0 | 36 | 1.6 | 37.2 | (-8.9, 64.5) |

* In Study 1 (NCT00539981) vaccine efficacy analyses were conducted on the Total Vaccinated Cohort (all randomized subjects who received study vaccine according to the treatment actually received and who provided data). Vaccine efficacy (VE) = 1 minus the ratio of Flublok/placebo infection rates.

†Determined under the assumption of Poisson event rates, according to Breslow and Day, 1987.

‡Meets CDC influenza-like illness (CDC-ILI) defined as fever of ≥100ºF oral accompanied by cough and/or sore throat, on the same day or on consecutive days.

§Primary endpoint of trial.

¶All culture-confirmed cases are considered, regardless of whether they qualified as CDC-ILI.

#Secondary endpoint of trial.

ÞExploratory (prespecified) endpoint of trial.

The efficacy of Flublok Quadrivalent is relevant to Flublok because both vaccines are manufactured using the same process and have overlapping compositions (see *Description [11]*).

Study 6 evaluated the efficacy of Flublok Quadrivalent in a randomized, observer-blind, active-controlled, multi-center trial conducted during the 2014-2015 influenza season in adults 50 years of age and older. A total of 8963 healthy, medically stable adults (mean age 62.5 years) were randomized in a 1:1 ratio to receive a single dose of Flublok Quadrivalent (n=4474) or a U.S.-licensed quadrivalent inactivated influenza vaccine (Comparator, Fluarix Quadrivalent, manufactured by Glaxo SmithKline) (n=4489).

Among randomized subjects, 58% were female, 80% white, 18% black/African-American, 2% other races, and 5% of Hispanic/Latino ethnicity. A total of 5186 (60%) subjects were 50-64 years of age and 3486 (40%) were ≥65 years of age. Real-time polymerase chain reaction (rtPCR) -confirmed influenza was assessed by active and passive surveillance for influenza-like illness (ILI) beginning 2 weeks post- vaccination until the end of the influenza season, approximately 6 months post- vaccination. ILI was defined as having at least one symptom (no specified duration) in each of two categories of respiratory and systemic symptoms. Respiratory symptoms included sore throat, cough, sputum production, wheezing and difficulty breathing. Systemic symptoms included fever > 99°F (>37°C) oral, chills, fatigue, headache and myalgia. For subjects with an episode of ILI, a nasopharyngeal swab sample was collected for rtPCR testing and reflex viral culture of rtPCR-positive samples.

The primary efficacy endpoint of Study 6 was rtPCR-positive, protocol-defined ILI due to any strain of influenza. Attack rates and relative vaccine efficacy (rVE), defined as 1 – [Attack rate Flublok Quadrivalent/ Attack Rate Comparator], were calculated for the total efficacy population (n=8604) for the primary efficacy endpoint and for several alternative efficacy endpoints (Table 5). Antigenic and phylogenetic evaluations of the similarity ("matching") of clinical isolates to vaccine antigens were not performed. CDC epidemiological data for the 2014-2015 influenza season indicated that Influenza A (H3N2) viruses predominated and that most influenza A/H3N2 viruses were antigenically dissimilar while A/H1N1 and B viruses were antigenically similar to vaccine antigens.

**Table 5: Relative Vaccine Efficacy (rVE) of Flublok Quadrivalent versus Comparator against Laboratory-Confirmed Influenza, Regardless of Antigenic Similarity to Vaccine Antigens, Adults 50 Years of Age and Older, Study 6 (Efficacy Population)**[*,†]

| | Flublok Quadrivalent (N=4303) | | Comparator (N=4301) | | RR | rVE % (95% CI) |
|---|---|---|---|---|---|---|
| | n | Attack Rate % (n/N) | n | Attack Rate % (n/N) | | |
| All rtPCR-positive Influenza[‡] | 96 | 2.2 | 138 | 3.2 | 0.70 | 30 (10, 47) |
| All rtPCR-positive Influenza A[§] | 73 | 1.7 | 114 | 2.7 | 0.64 | 36 (14, 53) |
| All rtPCR-positive Influenza B[§] | 23 | 0.5 | 24 | 0.6 | 0.96 | 4 (-72, 46) |
| All Culture-confirmed Protocol-defined ILI[§,¶] | 58 | 1.3 | 101 | 2.3 | 0.57 | 43 (21, 59) |

Abbreviations: rtPCR=reverse transcriptase polymerase chain reaction; Comparator=U.S.-licensed quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline; n=number of influenza cases; N=number of subjects in treatment group; RR=relative risk (Attack Rate Flublok/Attack Rate IIV4); rVE = [(1-RR) x 100].

[*]Study 6 is registered as NCT02285998.

[†]Efficacy Population included all randomized subjects who received study vaccine and provided any follow-up documentation for influenza-like illness beginning at least 14 days post-vaccination. Excluded subjects with protocol deviations that could adversely affect efficacy.

[‡]Primary Analysis. All cases of rtPCR-confirmed influenza are included. Antigenic characterization and genetic sequencing to determine similarity of isolates to vaccine antigens were not performed. CDC surveillance data indicated that the majority of influenza A/H3N2 wild type viruses were antigenically distinct whereas influenza A/H1N1 and type B viruses were antigenically similar to vaccine antigens during the 2014-2015 season. Study 6 met the pre-specified success criterion for the primary endpoint (lower limit of the 2-sided 95% CI of vaccine efficacy for Flublok Quadrivalent relative to Comparator should be not less than -20%).

[§]*Post hoc* analyses. All cases of influenza A were A/H3N2. Cases of influenza B were not distinguished by lineage.

[¶]Culture of rtPCR-positive samples was performed in MDCK cells.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Flublok is supplied as a single-dose, 0.5 mL prefilled syringe in a 10 syringe carton.

| Presentation | Carton NDC Number | Components and NDC Number |
|---|---|---|
| Single-Dose Prefilled Syringe | 49281-724-10 | Ten 0.5 mL single-dose prefilled syringes [49281-724-88] |

### 16.2 Storage and Handling

- Store refrigerated between 2° and 8°C (36° and 46°F).
- Do not freeze. Discard if product has been frozen.
- Protect syringes from light.
- Do not use after expiration date shown on the label.

## 17 PATIENT COUNSELING INFORMATION

Inform the vaccine recipient of the potential benefits and risks of vaccination with Flublok. Inform the vaccine recipient that:

- Flublok contains non-infectious proteins that cannot cause influenza.
- Flublok stimulates the immune system to produce antibodies that help protect against influenza viruses contained in the vaccine but does not prevent other respiratory infections.

Instruct the vaccine recipient to report any adverse events to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS).

Provide the vaccine recipient with the Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to vaccination. These materials are available free of charge at the Centers for Disease Control (CDC) website (www.cdc.gov/vaccines).

Encourage women who receive Flublok while pregnant to notify Sanofi Pasteur Inc. sanofipasteurpregnancyregistry.com or by calling 1-800-822-2463 (1-800-VACCINE).

Instruct the vaccine recipient that annual vaccination to prevent influenza is recommended.

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This product's labeling may have been updated. For the most recent prescribing information, please visit https://dailymed.nlm.nih.gov/dailymed/.