INDICATIONS AND USAGE

Flublok Quadrivalent is a vaccine indicated for active immunization against disease caused by influenza A subtype viruses and influenza type B viruses contained in the vaccine. Flublok Quadrivalent is approved for use in persons 18 years of age and older. (1)

DOSE AND ADMINISTRATION

For intramuscular (IM) injection only (0.5 mL). (2)

DOSAGE FORMS AND STRENGTHS

A sterile solution for injection supplied in 0.5 mL single dose prefilled syringes. (3)

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine. (4, 6.2, 11)

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*Sections or subsections omitted from the full prescribing information are not listed
Study 2 included 8672 subjects 50 years of age and older for safety analysis, randomized to receive Flublok Quadrivalent or Comparator. Among adults 18-49 years of age (Study 1), through 6 months post-vaccination, no deaths were reported. SAEs were reported by 12 subjects, 10 (1%) Flublok Quadrivalent recipients and 2 (0.6%) Comparator recipients. No SAEs were considered related to study vaccine.

Among adults 50 years of age and older (Study 2), 20 deaths occurred in the 6 months post-vaccination period, including 8 Flublok Quadrivalent and 12 Comparator recipients. No deaths were considered related to study vaccine. SAEs were reported by 145 (3.4%) Flublok Quadrivalent recipients and 132 (3%) Comparator recipients. No SAEs were considered related to study vaccine.

In the 28 days following vaccination, one or more unsolicited treatment emergent adverse events occurred in 10.3% of Flublok Quadrivalent recipients and 9.1% of Comparator recipients in Study 1 (adults 18-49 years of age) and in 13.9% of Flublok Quadrivalent and 14.1% of Comparator recipients in Study 2 (adults ≥50 years of age). In both studies, rates of individual events were similar between treatment groups, and most events were mild to moderate in severity.

The safety experience with Flublok is relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see Description (11)]. Flublok (trivalent formulation) has been administered to and safety data collected from a total of 4547 subjects in five clinical trials (Studies 3-7). 2497 adults 18 through 49 years, 972 adults 50 through 64 years, and 1078 adults 65 years and older. In Studies 3-5 and 7, SAEs were collected for 6 months post-vaccination. Study 6 collected SAEs through 30 days following receipt of vaccine. Study 6 also actively solicited pre-specified common hypersensitivity-type reactions through 30 days following receipt of vaccine. Analyses of SAEs were based on the 4547 subjects included in Flublok and Comparator study cohorts, regardless of whether subjects were included in the reactogenicity populations or the reactogenicity sub-populations [see Additional Table 6].

Adverse Reactions

Fever defined as ≥100°F. Grade 1 = No interference with activity. Grade 2 = Prevented some activities, and headache may have required non-narcotic pain reliever. Grade 3 = Prevented most or all normal activities, and headache may have required narcotic pain reliever. Grade 4 = Prevented all activities, and headache may have required medical attention.

Serious Adverse Events

Among 2497 adults 18-49 years of age (Studies 3 and 7 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 (pneumococcal meningitis) in a Flublok recipient was assessed as possibly related to the vaccine.

Among 972 adults 50-64 years of age (Studies 4 and 6 pooled), through up to 6 months post-vaccination, no deaths occurred, and SAEs were reported by 10 subjects, 6 Flublok recipients and 4 Comparator recipients. One of the SAEs, vasovagal syncope following injection of Flublok, was considered related to administration of study vaccine.

Among 1078 adults 65 years of age and older (Studies 5 and 6), through up to 6 months post-vaccination, 4 deaths occurred, 2 in Flublok recipients and 2 in Comparator recipients. None were considered related to the study vaccines. SAEs were reported by 80 subjects (37 Flublok recipients, 43 Comparator recipients). None were considered related to the study vaccines. Among 696 subjects aged 65 years and older (Study 7), 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 Comparator recipients reported such events over the 30 day follow-up period. A total of 1.9% and 0.9% of Flublok and Comparator recipients reported such reactions over the 30 day follow-up period.
Each 0.5 mL dose of Flublok Quadrivalent may also contain residual amounts of baculovirus and syringes contain no natural rubber latex. (Spodoptera frugiperda)

Data from an efficacy study (Study 2), which included 1759 subjects 8.5 Geriatric Use

that Flublok (trivalent formulation) would not be effective in children younger than 3 years of age. Safety compared to a U.S.-licensed influenza vaccine approved for use in this population, strongly suggesting

Pregnancy Exposure

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancy are 2% to 4% and 15% to 20%, respectively. Available data on Flublok Quadrivalent and Flublok (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnant women.

There were no developmental studies of Flublok Quadrivalent formulation performed in animals. The developmental and reproductive effects of Flublok (trivalent formulation) are relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions. A developmental study of Flublok (trivalent formulation) has been performed in rats administered 0.5 mL divided of Flublok (trivalent formulation) prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to Flublok (trivalent formulation) (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

Animal

In a developmental toxicity study, female rats were administered 0.5 mL divided of Flublok (trivalent formulation) by intramuscular injection twice prior to mating (35 days and 14 days prior to mating) and on gestation Day 8. No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

8.2 Lactation

Risk Summary

It is not known whether Flublok Quadrivalent is excreted in human milk. Data are not available to assess the effects of Flublok (trivalent formulation) or Flublok Quadrivalent on the breastfed infant or on milk production/excretion.

The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for Flublok Quadrivalent and any potential adverse effects on the breastfed child 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 decreased hemagglutination inhibition (HI) responses to Flublok (trivalent formulation) compared to a U.S.-licensed influenza vaccine approved for use in this population, strongly suggesting that Flublok (trivalent formulation) would not be effective in children younger than 3 years of age. Safety and effectiveness of Flublok Quadrivalent have not been established in children 3 years to less than 15 years of age.

8.5 Geriatric Use

Data from an efficacy study (Study 2), 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 Trials Experience (14.1) and Clinical Studies (14)).

11 DESCRIPTION

Flublok Quadrivalent [Quadrivalent Influenza Vaccine] is a sterile, clear, colorless solution of recombinant hemagglutinin (HA) proteins from four influenza viruses for intramuscular injection. It contains purified HA proteins produced in a continuous insect cell line (expressSF™) that is derived from SF9 cells of the fall armyworm (Autographa california nuclear polyhedrosis virus), extracted from the cells with Triton X-100 and further purified by column chromatography. The purified HA proteins are then blended and filled into single-dose syringes.

Flublok Quadrivalent is standardized according to United States Public Health Service (USPHS) requirements. For the 2022-2023 influenza season it is formulated to contain 160 mcg HA per 0.5 mL dose, with 45 mcg HA of each of the following 4 influenza virus strains: A/ Wisconsin/598/2019 (H1N1), A/ Darwin/8/2021 (H5N2), B/ Australia/135941/7/2021 and B/ Phuket/507/2013. A single 0.5 mL dose of Flublok Quadrivalent contains sodium chloride (4.4 mg), monobasic sodium phosphate (0.2 mg), dibasic sodium phosphate (0.5 mg), and polysorbate 20 (W700®) (27.5 mg). Each 0.5 mL dose of Flublok Quadrivalent may also contain residual amounts of baculovirus and Spodoptera frugiperda cell proteins (<19 mcg), baculovirus and cellular DNA (<20 ng), and Triton X-100 (<100 mcg).

Flublok Quadrivalent contains no egg proteins, antibiotics, or preservatives. The single-dose, prefilled syringes contain no natural rubber latex.
GlaxoSmithKline in a randomized, observer-blind, active-controlled, multicenter trial conducted during the 2014-2015 influenza season in healthy adults 18-49 years of age. A total of 1350 subjects were enrolled, randomized 3:1, and vaccinated with Flublok Quadrivalent (998 subjects) or Comparator (352 subjects). Subjects were predominantly female (85%), white (60%), black/African American (37%), and of non-Hispanic/Latino ethnicity (84%), with a mean age of 35.5 years. Of the total vaccinated population, 1292 subjects (98% of Comparator and 323 IVIVC recipients, respectively) were evaluable for immune responses (Immunogenicity Population).

Post-vaccination immunogenicity was evaluated on sera obtained 28 days after administration of a single dose of study vaccine. Hemagglutination inhibition (HI) geometric mean titer (GMTs) were compared for the two vaccine antigens. Immunogenicity was compared by calculating the difference in seroconversion rates (SCR) and the ratios of GMTs of Comparator to Flublok Quadrivalent. Seroconversion was defined as either a pre-vaccination HI titer of <1:10 and a post-vaccination HI titer of ≥1:40, or a pre-vaccination HI titer of ≥1:10 and a minimum 4-fold rise in post-vaccination HI titer, at Day 28.

Study 1 had eight co-primary endpoints: Day 28 HI seroconversion rates and GMTs for each of the four antigens contained in the study vaccines. GMTs were compared based on the upper bound of the two-sided 95% CI of the GMT ratio of Comparator to Flublok Quadrivalent. Success in meeting this endpoint was pre-defined as an upper bound (UB) of the two-sided 95% CI of GMT Comparator/GMT Flublok Quadrivalent ≤1.5. Flublok Quadrivalent met the success criterion for GMTs for three of the four antigens but not for the B/Victoria lineage antigen (Table 5).

Table 4: 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 2 (Efficacy Population)§

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Comparator/Flublok Quadrivalent, Fluarix Quadrivalent N=323</th>
<th>Flublok Quadrivalent N=969</th>
<th>rVE % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>1.00 (0.71, 1.90)</td>
<td>1.00 (0.74, 1.35)</td>
<td></td>
</tr>
<tr>
<td>A/H3N2</td>
<td>1.00 (0.71, 1.35)</td>
<td>1.00 (0.74, 1.35)</td>
<td></td>
</tr>
<tr>
<td>A/Yamagata</td>
<td>1.00 (0.71, 1.47)</td>
<td>1.00 (0.74, 1.35)</td>
<td></td>
</tr>
<tr>
<td>B/Victoria</td>
<td>1.00 (0.71, 1.35)</td>
<td>1.00 (0.74, 1.35)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

Study 1 is registered as NCT02205059.

The Immunogenicity Population included all randomized subjects who received a dose of study vaccine, provided serum samples for Day 0 and Day 28 within specified windows, and had no major protocol deviations that might adversely affect the immune response. The pre-defined success criterion for the GMT ratio of Comparator to Flublok Quadrivalent was that the upper bound of the two-sided 95% CI of the GMT ratio, GMT Comparator/ GMT Flublok Quadrivalent at 28 days post-vaccination, must not exceed 1.5.

†HI titers were assayed using egg-derived antigens.

Success in meeting the seroconversion rate (SCR) endpoint was pre-defined as an upper bound (UB) of the two-sided 95% CI of SCR Comparator – SCR Flublok Quadrivalent ≤10%. Flublok Quadrivalent met the success criterion for SCRs for three of the four antigens but not for the B/Victoria lineage antigen (Table 6). Sub-population analyses of immunogenicity did not reveal significant differences between genders. Sub-analyses according to race and ethnicity were not informative because the sizes of the subgroups were insufficient to reach meaningful conclusions. The HI response to the B/Victoria lineage antigen was low in both vaccine groups.

Table 5: Comparison of Day 28 Post-Vaccination Geometric Mean Titers (GMT) for Flublok Quadrivalent and Comparator in Adults 18-49 Years of Age, Study 1 (Immunogenicity Population)†‡§

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Comparator/Flublok Quadrivalent, Fluarix Quadrivalent N=323</th>
<th>Flublok Quadrivalent N=969</th>
<th>SCR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>1.00 (0.71, 1.90)</td>
<td>1.00 (0.74, 1.35)</td>
<td>0.81 (0.71, 0.92)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>1.00 (0.71, 1.35)</td>
<td>1.00 (0.74, 1.35)</td>
<td>0.86 (0.74, 0.99)</td>
</tr>
<tr>
<td>B/Victoria</td>
<td>1.00 (0.71, 1.35)</td>
<td>1.00 (0.74, 1.35)</td>
<td>1.49 (1.29, 1.71)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

Study 1 is registered as NCT02205059.

The Immunogenicity Population included all randomized subjects who received a dose of study vaccine, provided serum samples for Day 0 and Day 28 within specified windows, and had no major protocol deviations that might adversely affect the immune response. The pre-defined success criterion for the GMT ratio of Comparator to Flublok Quadrivalent was that the upper bound of the two-sided 95% CI of the GMT ratio, GMT Comparator/ GMT Flublok Quadrivalent at 28 days post-vaccination, must not exceed 1.5.

†HI titers were assayed using egg-derived antigens.

§Comparator: U.S.-licensed quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline.

14.2 Immunogenicity of Flublok Quadrivalent

Study 1 evaluated the immunogenicity of Flublok Quadrivalent as compared to a U.S.-licensed quadrivalent inactivated influenza vaccine (Comparator) (Fluarix Quadrivalent, manufactured by GlaxoSmithKline, manufactured by...
16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
Flublok Quadrivalent is supplied as a single-dose, 0.5 mL syringe in a 5 or 10 syringe carton:

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Carton NDC Number</th>
<th>Components and NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-Dose Prefilled</td>
<td>49281-722-10</td>
<td>Ten 0.5 mL single-dose prefilled syringes [NDC 49281-722-88]</td>
</tr>
</tbody>
</table>

16.2 Storage and Handling
- Store refrigerated between 2°C and 8°C (36°F 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 Quadrivalent.
Inform the vaccine recipient that:
- Flublok Quadrivalent contains non-infectious proteins that cannot cause influenza.
- Flublok Quadrivalent stimulates the immune system to produce antibodies that help protect against
  the influenza viruses carrying the proteins 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 or Flublok Quadrivalent while pregnant to notify Sanofi Pasteur
Inc. by calling 1-800-822-2463.
Instruct the vaccine recipient that annual vaccination to prevent influenza is recommended.

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