PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Supemtek™

Quadrivalent Recombinant Influenza Vaccine

Each 0.5 mL dose contains 45 mcg haemagglutinin of each

Influenza Virus Type A (H1N1), Type A (H3N2), Type B (Victoria) and Type B (Yamagata) strains

Solution for Intramuscular Injection

Active Immunizing Agent for the Prevention of Influenza

ATC Code: J07B B02

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

- Supemtek™ vaccine is indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B virus lineages contained in the vaccine. Supemtek is approved for use in persons 18 years of age and older[1].

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥50 years of age): Based on the data submitted and reviewed by Health Canada, the safety and immunogenicity of Supemtek in geriatric patients has been established; therefore, Health Canada has authorized an indication for geriatric use.

2 CONTRAINDICATIONS

Supemtek vaccine is contraindicated in patients who are hypersensitive to this vaccine or to any component of the vaccine. For a complete listing, 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Recommended recombinant influenza vaccine dosage

Age	Dosage	Number of doses
≥18 years of age	0.5 mL	1 (annually)

Health Canada has not authorized an indication for pediatric use in children less than 18 years of age.

[1] The National Advisory Committee on Immunization (NACI) provides additional guidance on the use of the influenza vaccine in Canada. Please refer to the published Statement on Seasonal Influenza Vaccine for the current season.

4.4 Administration

Supemtek is a sterile aqueous solution for injection. Inspect for extraneous particulate matter and/or discolouration before use. If these conditions exist, the product should not be administered.

Administration should be carried out by intramuscular (IM) route. Injections of Supemtek vaccine should be administered intramuscularly, preferably in the deltoid muscle.

Do not administer this product intravenously.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 1: Dosage Forms, Strengths, and Non-medicinal Ingredients

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Intramuscular injection	**Dosage Form:** Solution for injection **Active Ingredients:** Each 0.5 mL dose contains 45 mcg hemagglutinin (HA) of each strain listed below (see Description)	Dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 20 (Tween®20), sodium chloride Baculovirus and *Spodoptera frugiperda* cell proteins, Baculovirus and cellular DNA and Triton X-100.

Description

Supemtek is a sterile aqueous solution of recombinant influenza hemagglutinin for intramuscular injection containing purified HA proteins produced in a continuous insect cell line (expresSF+®) 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 four HAs is expressed in this cell line using a baculovirus vector (*Autographa californica* nuclear polyhedrosis virus, ACNPV), extracted from the cells with Triton X-100 and further purified by column chromatography and diafiltration against phosphate-buffered saline. The purified HAs are then blended and filled into single-dose pre-filled syringes.

Supemtek is a quadrivalent recombinant influenza vaccine (RIV4) and is formulated to contain 180 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 45 mcg HA of each of the four strains for the 2022-2023 season listed below:

A/Wisconsin/588/2019 (H1N1)pdm09 - like strain (A/Wisconsin/588/2019)

A/Darwin/6/2021 (H3N2) - like strain (A/Darwin/6/2021)

B/Austria/1359417/2021 - like strain (B/Austria/1359417/2021)

B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013)

Supemtek vaccine is supplied as a sterile solution in a pre-filled syringe. Supemtek after shaking the syringe well, is clear and colorless without visible particulates

Composition

The composition and function of each component contained within the 0.5 mL single dose are provided in Table 2. Supemtek does not contain egg proteins, antibiotics, or preservatives. There is no gelatin added in Supemtek as a stabilizer.

Table 2: Composition of the Drug Product

Component	Quantity (per 0.5 mL dose)	Function
Purified hemagglutinin (HA):	**180 mcg total**	
A (H3N2)	45 mcg HA	Active substance
A (H1N1)	45 mcg HA	Active substance
B (Victoria lineage)	45 mcg HA	Active substance
B (Yamagata lineage)	45 mcg HA	Active substance
Other:		
Sodium chloride	4.4 mg	Excipient
Monobasic sodium phosphate	0.2 mg*	Excipient
Dibasic sodium phosphate	0.5 mg*	Excipient
Polysorbate 20 (Tween®20)	27.5 mcg	Stabilizer/Excipient
Baculovirus and *Spodoptera frugiperda* cell proteins	≤ 19 mcg	Residual
Baculovirus and cellular DNA	≤ 10 ng	Residual
Triton X-100	≤ 100 mcg	Residual

*calculated from the anhydrous form

Packaging

Supemtek is supplied as single dose pre-filled syringes. See Table 3. The syringes do not contain natural rubber latex.

Table 3: Final Product Container

Containers and devices	Container element	Nature
Syringe without needle	1.5 mL *Luer-Lok*® syringe	Type I borosilicate glass
	Plunger stopper and Plunger rod	Butyl, latex-free
	Tip cap	Latex-free

7 WARNINGS AND PRECAUTIONS

General

Managing Allergic Reactions

Caution should be exercised when the vaccine is administered to subjects with hypersensitivity to the vaccine itself or any of its components. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Limitations of Vaccine Effectiveness

Vaccination with Supemtek may not protect 100% of vaccine recipients.

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed.

Immune

Altered Immunocompetence

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

Neurologic

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk 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 1 additional case per 1 million persons vaccinated.

If Guillain - Barré Syndrome has occurred within 6 weeks following previous influenza vaccination, the decision to give Supemtek should be based on careful consideration of the potential benefits and risks.

Psychiatric

Syncope

Syncope (fainting) has been reported following vaccination with Supemtek. Procedures should be in place to prevent falling injury and to manage syncopal reactions to any intramuscular injection.

7.1 Special Populations

7.1.1 Pregnant Women

There is limited amount of data from the use of Supemtek in pregnant women.

One animal study performed with trivalent recombinant influenza vaccine (RIV3) did not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development or early post-natal development. An assessment of the risks and benefits should be performed by a health care professional before administering Supemtek to pregnant women[2].

7.1.2 Breast-feeding

It is not known whether Supemtek vaccine is excreted in human milk. An assessment of the risks and benefits should be performed by a health care professional before administering Supemtek to a nursing woman.

7.1.3 Pediatrics

Pediatrics (less than 18 years): Safety and immunogenicity of Supemtek has not been established in individuals less than 18 years of age.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under widely varying conditions, and because the strain composition of influenza vaccines is subject to annual changes, adverse reaction rates observed in the clinical trial(s) of one vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

RIV4 has been administered to and safety data collected from 998 adults 18-49 years of age (Study 1) and 4328 adults 50 years of age and older (Study 2). Both studies were Phase 3, multi- center, randomized, active-controlled, double-blind trials.

Study 1 (in adults 18-49 years of age): The most common reactions occurring after vaccine administration were injection-site reactions (tenderness and pain) reported overall by 48% and 37% of study participants 18-49 years of age receiving RIV4, respectively and 47% and 36% respectively of those receiving the active comparator vaccine (Table 4).

[2] NACI provides additional information on the use of influenza vaccines in pregnant women. Please refer to the most current NACI recommendations for pregnant women.

Table 4: Frequency of Solicited Injection Site and Systemic Adverse Reactions within 7 Days of Administration of RIV4 or Comparator[1] in Adults 18-49 Years of Age, Study 1 (Reactogenicity Populations)[1, 2]

Reactogenicity Term	RIV4 N=996 %			Comparator N=332 %		
	Any Grade[6]	Grade 3	Grade 4	Any Grade[6]	Grade 3	Grade 4
Subjects with ≥1 injection site reaction[3, 4]	51	1	0	52	2	0
Local Tenderness	48	1	0	47	1	0
Local Pain	37	1	0	36	1	0
Firmness / Swelling	5	0	0	3	0	0
Redness	4	0	0	1	0	0
Subjects with ≥1 systemic reaction[3,5]	34	2	<1	36	3	<1
Headache	20	1	0	21	2	<1
Fatigue	17	1	0	17	1	0
Muscle Pain	13	1	0	12	1	0
Joint Pain	10	1	0	10	1	0
Nausea	9	1	<1	9	1	0
Shivering / Chills	7	1	0	6	1	0
Fever[6, 7]	2	<1	0	1	<1	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%.

[1] Comparator = U.S.-licensed comparator quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline.

[2] Study 1 is registered as NCT02290509 under the National Clinical Trials registry.

[3] Reactogenicity Populations were defined as all randomized subjects who received study vaccine according to the treatment actually received and who had at least one non-missing data point for injection site, systemic or body temperature reactogenicity categories. For local pain, tenderness and systemic reactions: Grade 1 = No interference with activities. Grade 2 = Prevented some activities, and headache may have required non-narcotic pain reliever. Grade 3 = Prevented most or all normal activities or required prescription medications. Grade 4 = Required visit to ER or hospitalization. For injection site redness and firmness/swelling: Grade 1=25 to ≤50 mm (small). Grade 2=51 to ≤100 mm (medium). Grade 3=>100 mm (large). Grade 4=necrosis or exfoliative dermatitis.

[4] Denominators for injection site reactions: RIV4 n = 996, Comparator n =332.

[5] Denominators for systemic reactions: RIV4 n = 994, Comparator n = 332.

[6] Denominators for fever: RIV4 n = 990, Comparator n = 327.

[7] Fever defined as body temperature ≥38°C. Grade 1 (≥38°C to ≤38.3°C); Grade 2 (38.4°C to ≤ 38. 8°C); Grade 3 (38.9°C to ≤40°C); Grade 4 >40°C.

Study 2 (in adults 50 years of age and older): In study participants 50 years of age and older, injection site tenderness was reported by 34% and 37% of those receiving RIV4 or active comparator, respectively Table 5). Onset usually occurred within the first 3 days after vaccination. All resolved without sequelae.

Table 5: Frequency of Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of RIV4 or Comparator[1] in Adults 50 Years of Age and Older, Study 2 (Reactogenicity Populations) [2, 3]

Reactogenicity Term	RIV4 N=4312 %			Comparator N=4327 %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Subjects with ≥1 injection site reaction[3, 4]	38	<1	<1	40	<1	<1
Local Tenderness	34	<1	<1	37	<1	<1
Local Pain	19	<1	0	22	<1	<1
Firmness / Swelling	3	<1	0	3	<1	0
Redness	3	<1	0	2	<1	0
Subjects with ≥1 systemic reactogenicity event[3,5]	25	1	<1	26	1	<1
Headache	13	<1	<1	14	1	<1
Fatigue	12	<1	0	12	<1	<1
Muscle Pain	9	<1	<1	9	<1	<1
Joint Pain	8	<1	0	8	<1	<1
Nausea	5	<1	0	5	<1	<1
Shivering / Chills	5	<1	0	4	<1	<1
Fever[6,7]	<1	<1	0	1	<1	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%.

[1]Comparator = U.S.-licensed comparator quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline.

[2] Study 2 is registered as NCT02285998 under the National Clinical Trials registry.

[3] Reactogenicity Populations were defined as all randomized subjects who received study vaccine according to the treatment actually received and who had at least one non-missing data point for injection site, systemic or body temperature reactogenicity categories. For local pain, tenderness, and systemic reactions: Grade 1=No interference with activity. Grade 2=Some interference with activity. Grade 3=Prevents daily activity. Grade 4=Required ER visit or hospitalization. For injection site redness and firmness/swelling: Grade 1=25 to ≤50 mm (small). Grade 2=51 to ≤100 mm (medium); Grade 3=>100 mm (large); Grade 4=necrosis or exfoliative dermatitis.

[4] Denominators for injection site reactions: RIV4 n = 4307, Comparator n = 4319.

[5] Denominators for systemic reactions: RIV4 n = 4306, Comparator n = 4318.

[6] Denominators for fever: RIV4 n = 4262, Comparator n = 4282.

[7] Fever defined as body temperature ≥38°C. Grade 1 (≥38°C to ≤38.3°C); Grade 2 (38.4°C to ≤ 38.8°C); Grade 3 (38.9°C to ≤40°C); Grade 4 >40°C.

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%) RIV4 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, including 8 RIV4 and 12 Comparator recipients. No deaths were considered related to study vaccine. SAEs were reported by 145 (3.4%) RIV4 recipients and 132 (3%) Comparator recipients. No SAEs were considered related to study vaccine.

In the 28 days following vaccination, one or more unsolicited adverse events occurred in 10.3% of RIV4 and 10.5% of Comparator recipients in Study 1 (adults 18-49 years of age) and in 13.9% of RIV4 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.

8.5 Post-Market Adverse Reactions

The following adverse events have been reported during the post-marketing use of RIV4. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

- Immune system disorders: anaphylaxis, anaphylactoid reactions, allergic reactions, and other forms of hypersensitivity.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Concomitant Vaccine Administration

Supemtek should not be mixed with another vaccine in the same syringe or vial.

No data to assess the concomitant administration of Supemtek with other vaccines is available. If Supemtek is to be given at the same time as another injectable vaccine(s), the vaccine(s) should be administered at different injection sites.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Supemtek contains recombinant HA proteins of the four 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 that is known to protect against influenza infection. Using the recombinant production technology, the HA in Supemtek has an identical primary structure to the HA in the wild type virus strains selected for seasonal vaccines.

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. Therefore, influenza vaccines are standardized to contain the hemagglutinins of influenza virus strains (i.e., typically two type A and two type B), representing the influenza viruses likely to be circulating in the upcoming season.

Annual influenza vaccination is recommended because immunity during the year after vaccination declines and because circulating strains of influenza virus change from year to year.

10.2 Pharmacodynamics

Refer to 14 CLINICAL TRIALS section for immunogenicity.

10.3 Pharmacokinetics

No pharmacokinetic studies have been performed.

11 STORAGE, STABILITY AND DISPOSAL

Store at 2°C to 8°C. Do not freeze.

Protect syringes from light.

12 SPECIAL HANDLING INSTRUCTIONS

Do not use after the expiration date shown on the label.

Any unused product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Quadrivalent Recombinant Influenza Vaccine

Product Characteristics

Supemtek is a sterile aqueous solution of recombinant influenza hemagglutinin for intramuscular injection containing purified HA proteins produced in a continuous insect cell line (expresSF+®) 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 four HAs is expressed in this cell line using a baculovirus vector (*Autographa californica* nuclear polyhedrosis virus, ACNPV), extracted from the cells with Triton X-100 and further purified by column chromatography and diafiltration against phosphate-buffered saline. The purified HAs are then blended and filled into single-dose pre-filled syringes.

Supemtek is a quadrivalent recombinant influenza vaccine (RIV4). A single 0.5 mL dose of Supemtek 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 Supemtek may also contain residual amounts of baculovirus and *Spodoptera frugiperda* cell proteins (≤ 19 mcg), baculovirus and cellular DNA (≤ 10 ng), and Triton X-100 (≤ 100 mcg).

Supemtek does not contain egg proteins, antibiotics, or preservatives. The single-dose, pre-filled syringes contain no natural rubber latex. Gelatin is not added in Supemtek as a stabilizer.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Study 1

Study 1 evaluated the immunogenicity of RIV4 as compared to a U.S.-licensed quadrivalent inactivated influenza vaccine (Comparator) in a randomized, observer-blind, active-controlled, multi-center trial conducted during the 2014-2015 influenza season in healthy adults 18-49 years of age (12). A total of 1350 subjects were enrolled, randomized 3:1, and vaccinated with Supemtek (998 subjects) or Comparator (332 subjects). Subjects were predominantly female (65%), white (60%), black/African American (37%), and of non-Hispanic/Latino ethnicity (84%), with a mean age of 33.5 years. Of the total vaccinated population, 1292 subjects (969 RIV4 and 323 IIV4 recipients, respectively) were evaluable for immune responses (Immunogenicity Population).

Study 2

Study 2 evaluated the efficacy of RIV4 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 (11). 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 RIV4 (n=4474) or a U.S.-licensed quadrivalent inactivated influenza vaccine (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.

Study 3

Study 3 was conducted for trivalent recombinant influenza vaccine (RIV3). The efficacy of RIV3 is relevant to RIV4 because both vaccines are manufactured using the same process and have overlapping compositions.

The efficacy of RIV3 in protecting against 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 3).

Study 3 enrolled and vaccinated 4648 healthy adults (mean age 32.5 years) randomized in a 1:1 ratio to receive a single dose of RIV4 (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.

14.2 Study Results

14.2.1 Efficacy of Supemtek

Study 2 evaluated the efficacy of RIV4 in a randomized, observer-blind, active controlled, multi-center trial conducted during the 2014-2015 influenza season in the Unites States in adults 50 years of age and older.

A total of 8963 healthy, medically stable adults were randomized in a 1:1 ratio to receive a single dose of RIV4 (n=4474) or a U.S.-licensed quadrivalent inactivated influenza vaccine (n=4489). A total of 5412 (60.4%) subjects were 50-64 years of age and 3551 (39.6%) 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. A nasopharyngeal swab sample was collected for rtPCR testing from subjects with an episode of ILI. Reflex viral culture was performed on rtPCR-positive samples.

The primary efficacy endpoint of Study 2 was rtPCR-positive, protocol-defined ILI due to any strain of influenza. Antigenic and phylogenetic evaluations of the similarity ("matching") of clinical isolates to vaccine antigens were not performed. US 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.

Supemtek met the prespecified success criterion for non-inferiority to the comparator pre-defined as a lower bound of the two-sided 95% CI >-20%.

Table 6: Relative Vaccine Efficacy (rVE) of RIV4 versus Comparator against Laboratory-Confirmed Influenza, Regardless of Antigenic Similarity to Vaccine Antigens, Adults 50 Years of Age and Older, Study 2 (Efficacy Population) [1]

	RIV4 (N=4303)		Comparator (N=4301)		RR	rVE % (95% CI)
	n	Attack Rate % (n/N)	n	Attack Rate % (n/N)		
All rtPCR-positive Influenza [2]	96	2.2	138	3.2	0.70	30 (10, 47)
All rtPCR-positive Influenza A[3]	73	1.7	114	2.7	0.64	36 (14, 53)
All rtPCR-positive Influenza B[3]	23	0.5	24	0.6	0.96	4 (-72, 46)
All Culture-confirmed Protocol-defined ILI[3,4]	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 RIV4/Attack Rate IIV4); rVE = [(1-RR) x 100].

[1] 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 postvaccination. Excluded subjects with protocol deviations that could adversely affect efficacy.

[2] Primary Analysis. All cases of rtPCR-confirmed influenza are included.

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

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

14.2.2 Immunogenicity of Supemtek

The immunogenicity results from both Study 1 and Study 2 are summarized below.

Study 1 evaluated the immunogenicity of RIV4 as compared to a U.S.-licensed quadrivalent inactivated influenza vaccine (Comparator) in a randomized, observer-blind, active-controlled, multi-center trial conducted during the 2014-2015 influenza season in healthy adults 18-49 years of age. Of the total vaccinated population of 1350 subjects, 1292 subjects (969 RIV4 and 323 IIV4 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 titers (GMTs) were determined for the two vaccine groups for each vaccine antigen. Immunogenicity was compared by calculating the difference in seroconversion rates (SCR) and the ratios of GMTs of Comparator to RIV4. 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 RIV4. Success in meeting this endpoint was pre-defined as an upper bound (UB) of the two-sided 95% CI of $GMT_{Comparator} / GMT_{RIV4} \leq 1.5$. RIV4 met the success criterion for GMTs for three of the four antigens but not for the B/Victoria lineage antigen (Table 7).

Table 7: Comparison of Day 28 Post-Vaccination Geometric Mean Titers (GMT) for RIV4 and Comparator in Adults 18-49 Years of Age, Study 1 (Immunogenicity Population) [1, 2, 3, 4]

Antigen	Post-vaccination GMT RIV4 N=969	Post-vaccination GMT Comparator N=323	GMT Ratio Comparator/ RIV4 (95% CI)
A/H1N1	493	397	0.81 (0.71, 0.92)
A/H3N2	748	377	0.50 (0.44, 0.57)
B/Yamagata	156	134	0.86 (0.74, 0.99)
B/Victoria	43	64	1.49 (1.29, 1.71)

Abbreviations: CI, confidence interval; GMT, geometric mean titer.
[1] Study 1 is registered as NCT02290509.
[2] 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 RIV4 was that the upper bound of the 2-sided 95% CI of the GMT ratio, GMT Comparator / GMT RIV4 at 28 days post-vaccination, must not exceed 1.5.
[3] HI titers were assayed using egg-derived antigens.
[4] Comparator: U.S.-licensed quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline.

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 RIV4 ≤10%. RIV4 met the success criterion for SCRs for three of the four antigens but not for the B/Victoria lineage antigen (Table 8). 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 subsets were insufficient to reach meaningful conclusions. The HI response to the B/Victoria lineage antigen was low in both vaccine groups.

Table 8:Comparison of Day 28 Seroconversion Rates for RIV4 and Comparator in Adults 18-49 Years of Age, Study 1 (Immunogenicity Population) [1, 2, 3, 4]

Antigen	SCR (%, 95% CI) RIV4 N=969	SCR (%, 95% CI) Comparator N=323	SCR Difference (%) Comparator - RIV4 (95% CI)
A/H1N1	66.7 (63.6, 69.6)	63.5 (58.0, 68.7)	-3.2 (-9.2, 2.8)
A/H3N2	72.1 (69.2, 74.9)	57.0 (51.4, 62.4)	-15.2 (-21.3, -9.1)
B/Yamagata	59.6 (56.5, 62.8)	60.4 (54.8, 65.7)	0.7 (-5.4, 6.9)
B/Victoria	40.6 (37.4, 43.7)	58.2 (52.6, 63.6)	17.6 (11.4, 23.9)

Abbreviations: CI, confidence interval; SCR, seroconversion rate
Seroconversion was defined as a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥1:40 or a pre-vaccination HI titer ≥1:10 and a minimum four-fold rise in post-vaccination HI antibody titer.
[1]Study 1 is registered as NCT02290509.
[2] 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 SCR difference between Comparator and RIV4 was that the upper bound of the 2-sided 95% CI of the SCR difference IIV4 – RIV4 at 28 days post-vaccination, must not exceed 10%.
[3] HI titers were assayed using egg-derived antigens.
[4] Comparator: U.S.-licensed quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline.

Study 2 evaluated the immunogenicity of RIV4 as compared to a U.S.-licensed quadrivalent inactivated influenza vaccine (Comparator), as one of the secondary objectives. Pre- and post-vaccination (Day 28) HI titers from a subset of subjects (314 in RIV4 and 300 in IIV4 recipients, respectively) were analyzed.

The study 1 in adults 18-49 years was conducted in parallel to the study 2 in adults of 50 years of age and older. These adults 18-49 years were vaccinated during the same influenza season (2014-2015 Northern Hemisphere influenza season) and received the same RIV4 formulation (same vaccine strain composition) as adults of 50 years of age and older in the study 2. The immune response induced by RIV4 was assessed by the same HAI assay and performed by the same laboratory for both studies. Immunogenicity results in adults 18-49 years (Study 1) and adults ≥50 years (Study 2) are presented in Table 9 and Table 10 respectively.

Table 9: Summary of HAI Antibody Response to RIV4 for Each Strain in Adults 18-49 years (Study 1) - Immunogenicity Analysis Set

	Adults 18-49 years N=969
	GMT pre-vaccination (95% CI)
A/California/7/2009 (H1N1)	59 (54; 65)
A/Texas/50/2012 (H3N2)	74 (68; 82)
B/Massachusetts/02/2012 (Yamagata lineage)	26 (24; 29)
B/Brisbane/60/2008 (Victoria lineage)	12 (11; 13)
	GMT post-vaccination (95% CI)
A/California/7/2009 (H1N1)	493 (460; 527)
A/Texas/50/2012 (H3N2)	748 (700; 800)
B/Massachusetts/02/2012 (Yamagata lineage)	156 (145; 168)
B/Brisbane/60/2008 (Victoria lineage)	43 (40; 46)
	SCR % (95% CI)
A/California/7/2009 (H1N1)	66.7 (63.6; 69.6)
A/Texas/50/2012 (H3N2)	72.1 (69.2; 74.9)
B/Massachusetts/02/2012 (Yamagata lineage)	59.6 (56.5; 62.8)
B/Brisbane/60/2008 (Victoria lineage)	40.6 (37.4; 43.7)

N=number of subjects with available data for the considered endpoint
GMT: Geometric Mean Titer; CI: Confidence Interval; SCR: Seroconversion rate

Table 10: Summary of HAI Antibody Response to RIV4 for Each Strain in Adults ≥50 years (Study 2) - Immunogenicity Analysis Set

	Adults ≥50 years N=314
	GMT pre-vaccination (95% CI)
A/California/7/2009 (H1N1)	44 (38; 51)
A/Texas/50/2012 (H3N2)	87 (73; 103)
B/Massachusetts/02/2012 (Yamagata lineage)	17 (15; 20)
B/Brisbane/60/2008 (Victoria lineage)	14 (12; 15)
	GMT post-vaccination (95% CI)
A/California/7/2009 (H1N1)	190 (164; 221)
A/Texas/50/2012 (H3N2)	522(462; 589)
B/Massachusetts/02/2012 (Yamagata lineage)	55 (48; 64)
B/Brisbane/60/2008 (Victoria lineage)	29 (26; 33)
	SCR % (95% CI)
A/California/7/2009 (H1N1)	44.9 (39.3; 50.6)
A/Texas/50/2012 (H3N2)	54.5 (48.8; 60.1)
B/Massachusetts/02/2012 (Yamagata lineage)	38.9 (33.4; 44.5)
B/Brisbane/60/2008 (Victoria lineage)	21.0 (16.6; 25.9)

N=number of subjects with available data for the considered endpoint
GMT: Geometric Mean Titer; CI: Confidence Interval; SCR: Seroconversion rate

14.2.3 Efficacy of trivalent recombinant influenza vaccine (RIV3)

The efficacy of trivalent recombinant influenza vaccine (RIV3) is relevant to RIV4 because both vaccines are manufactured using the same process and have overlapping compositions.

The efficacy of trivalent recombinant influenza vaccine in protecting against influenza illness was evaluated in a randomized, observer-blind, placebo-controlled multicenter trial conducted in the United States during the 2007-2008 influenza season in adults 18-49 years of age (Study 3).

Study 3 enrolled and vaccinated 4648 healthy adults randomized in a 1:1 ratio to receive a single dose of RIV3 (n=2344) or saline placebo (n=2304).

Culture-confirmed influenza was assessed by active and passive surveillance for influenza-like illness (see formal definition below) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 7 months post- vaccination.

The primary efficacy endpoint of Study 3 was defined as an influenza-like illness meeting the case definition of CDC-ILI with a positive culture for an influenza virus strain antigenically resembling a strain represented in RIV3. CDC-ILI is defined as fever of ≥100°F (37.8°C) oral accompanied by cough, sore throat, or both, on the same or consecutive days. Attack rates and vaccine efficacy (VE), defined as the reduction in the influenza rate for RIV3 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 3 were not antigenically matched to the strains represented in the vaccine. Therefore, an exploratory analysis of VE of RIV3 against all strains, regardless of antigenic match to the vaccine, isolated from subjects with "any ILI", defined as not necessarily meeting CDC-ILI criteria was done and demonstrated an efficacy estimate of 44.8% (95% CI 24.4, 60.0). See Table 11 for VE by case definition.

Table 11:Vaccine Efficacy Against Culture-Confirmed Influenza in Healthy Adults 18-49 Years of Age, Study 3*

Case definition	RIV3 (N=2344)		Saline Placebo (N=2304)		RIV3 Vaccine Efficacy [1] -%	95% Confidence Interval
	Cases, n	Rate, %	Cases, n	Rate, %		
Positive culture with a strain represented in the vaccine						
CDC-ILI, all matched strains [2, 3]	1	0.04	4	0.2	75.4	(-148.0, 99.5)
Any ILI, all matched strains [4, 5]	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 [2, 6]	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 [4, 6]	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 3 (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 Supemtek /placebo infection rates.

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

[2] 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.

[3] Primary endpoint of trial.

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

[5] Secondary endpoint of trial.

[6] Exploratory endpoint of trial.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Supemtek has not been evaluated in non-clinical studies.

A developmental toxicity study conducted in rats vaccinated with the trivalent recombinant influenza vaccine (RIV3) revealed no evidence of impaired female fertility.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Supemtek™

Quadrivalent Recombinant Influenza Vaccine

Read this carefully before you start taking Supemtek and each time you get a dose. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Supemtek.

What is Supemtek used for?

Supemtek is a protein-based vaccine used to prevent influenza. This vaccine may be given to adults 18 years and older.

Influenza (or flu) is an infection caused by the influenza virus. Flu symptoms can include fever, headache, muscle pain, runny nose, sore throat, extreme tiredness and cough. Some people, such as children, older adults, and those with chronic medical conditions, can get much sicker. Flu is a disease that can spread rapidly and is caused by different types of strains that can change every year. This is why you might need to be vaccinated every year.

The National Advisory Committee on Immunization (NACI) encourages annual influenza vaccination for all Canadians who are able to have the vaccine, especially for particular groups of people at high risk of influenza-related complications or hospitalization.

How does Supemtek work?

Supemtek causes your body to produce its own natural protection against influenza virus. After you receive the vaccine, your body begins to make substances called antibodies against the strains of virus that are in the vaccine. Antibodies help your body to fight disease and are effective for the duration of the flu season. When you are exposed to the virus, the antibodies will help to keep you from getting sick. If you do get the flu, you may not be as sick. SUPEMTEK™ has been used by many people to lower their risk of catching the flu.

What are the ingredients in Supemtek?

This vaccine complies with the World Health Organisation (WHO) recommendation (Northern hemisphere) for the 2022-2023 season.

Medicinal ingredients:
Each 0.5 mL dose of the vaccine contains 45 mcg haemagglutinin (HA) of purified recombinant protein generated from the genetic sequences from each of the following influenza virus strain types:

A/Wisconsin/588/2019 (H1N1)pdm09 - like strain (A/Wisconsin/588/2019)
A/Darwin/6/2021 (H3N2) - like strain (A/Darwin/6/2021)
B/Austria/1359417/2021 - like strain (B/Austria/1359417/2021)
B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013)

Non-medicinal ingredients: sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate and polysorbate 20.

Supemtek does not contain adjuvant.

Supemtek's production method for recombinant proteins does not use eggs, therefore, there are no egg proteins in the vaccine.

Supemtek does not contain any antibiotics or preservatives. It is latex-free.

There is no gelatin added in Supemtek as a stabilizer.

Supemtek comes in the following dosage forms:

Supemtek is a liquid vaccine that is injected into a muscle. A single dose is 0.5 mL.

Do not use Supemtek if:

- You have a known severe allergy to any ingredient in Supemtek or you have had a severe allergic reaction after receiving a vaccine that contained similar ingredients.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Supemtek. Talk about any health conditions or problems you may have, including if you:

- Have a high fever or serious illness. Vaccination may be delayed until your fever is gone.
- Have an allergy to any component of the vaccine.
- You have a poor immune response (immunodeficiency or taking medicines affecting the immune system e.g. medicine against cancer (chemotherapy) or corticosteroid medicines).
- You have a bleeding problem or bruise easily.
- Fainting can occur following, or even before, any needle injection, therefore tell the doctor or nurse if you fainted with a previous injection.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Supemtek:

Supemtek is given by a doctor, pharmacist, or nurse as a 0.5 ml injection in the muscle in the upper arm or in the thigh depending on your age and muscle mass.

Usual dose:

A single dose is 0.5 mL.
The vaccination should be given in the muscle, preferably in the deltoid (shoulder) region.

Overdose:

If you think you, or a person you are caring for, have taken too much Supemtek, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Not applicable to this vaccine.

What are possible side effects from using Supemtek?

Like all medicines, this vaccine can cause side effects, although not everybody gets them. These are not all the possible side affects you may feel when taking Supemtek. If you experience any side effect not listed here, contact your healthcare professional.

Allergic reactions
Contact your doctor or healthcare professional immediately or go to the nearest hospital emergency room right away if you experience allergic reactions that may be life-threatening.

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional**	
	Only if severe	**In all cases**
Allergic reactions Symptoms may include difficulty breathing, shortness of breath, swelling of the face, lips, throat or tongue, cold, clammy skin, palpitations, dizziness, weakness, fainting, rash or itching.		✓

The following side effects have been reported with Supemtek:

Very common (may affect more than 1 in 10 people):

- Local reactions: pain, tenderness
- Fatigue
- Headache
- Muscle pain and joint pain (in adults 18-49 years of age)

Common (may affect up to 1 in 10 people):

- Feeling sick (nausea)
- Local reactions: redness, swelling, hardness (induration) around the area where the vaccine is injected
- Fever (> 38°C) (in adults 18-49 years of age)
- Shivering
- Muscle pain and joint pain (in adults 50 years of age and older)

Uncommon (may affect up to 1 in 100 people):

- Fever (> 38°C) (in adults 50 years of age and older)

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Sanofi Pasteur cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Store Supemtek in a refrigerator at 2° to 8°C. **Do not freeze.** Throw the product away if it has been exposed to freezing.

Protect syringes from light.

Do not use after the expiration date.

Keep out of reach and sight of children.

If you want more information about Supemtek:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html) the manufacturer's website www.sanofi.ca, or by calling 1-888-621-1146 (no charge).

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