INTANZA™

Influenza Vaccine (Split Virion, Inactivated)

Suspension for Injection

For active immunization against Influenza

ATC Code: J07B B02

Manufactured by:
Sanofi Pasteur SA
Lyon, France

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration

Intradermal injection.

Dosage Form/Strength

Suspension for injection.

Each 0.1 mL dose is formulated to contain:

Active Ingredients

9 µg of influenza virus haemagglutinin antigens (HA) of each strain listed in the DESCRIPTION section.

or

15 µg of influenza virus haemagglutinin antigens (HA) of each strain listed in the DESCRIPTION section.

Clinically Relevant Non-Medicinal Ingredients

Manufacturing process residuals: neomycin, formaldehyde, ovalbumin and Triton® X-100 may be present in trace amounts.

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

DESCRIPTION

INTANZA™ [Influenza Vaccine (Split Virion, Inactivated)] is a sterile, colourless and opalescent suspension containing 3 strains of influenza virus cultivated on embryonated eggs, concentrated, purified by zonal centrifugation in a sucrose gradient, split by Triton® X-100, inactivated by formaldehyde, concentrated and then diluted in phosphate buffered saline solution. The type of viral antigens contained in INTANZA™ conform to the current requirements of the World Health Organization (WHO). (1) The strains for the 2010 - 2011 season are: A/California/7/2009 (H1N1)-like strain, A/Perth/16/2009 (H3N2)-like strain and B/Brisbane/60/2008.

INDICATIONS AND CLINICAL USE

INTANZA™ is indicated for active immunization against influenza caused by the specific strains of influenza virus contained in the vaccine in adults from 18 years of age and over. The vaccine is provided in two different strengths with specific indications:

- 9 µg/strain/0.1 mL in adults from 18 to 59 years of age, and
- 15 µg/strain/0.1 mL in individuals 60 years of age and over.

Although the current influenza vaccine can contain one or more of the antigens administered in previous years, annual vaccination using the current vaccine is necessary because immunity declines in the year following vaccination.

NACI encourages annual influenza vaccination for all Canadians who have no contraindications. (2)

Vaccine should be offered up to and even after influenza virus activity is documented in a community. (2) (3)

Pediatrics

INTANZA™ is not indicated for persons less than 18 years of age.

Geriatrics

INTANZA™ 15 µg is indicated in persons 60 years of age and over.

CONTRAINDICATIONS

Hypersensitivity

INTANZA™ should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine (see DOSAGE FORMS, COMPOSITION AND PACKAGING - Composition) or after previous administration of the vaccine or a vaccine containing the same components or constituents.

WARNINGS AND PRECAUTIONS

General

Before administration of INTANZA™, health-care providers should inform the recipient of the benefits and risks of immunization, inquire about the recent health status of the recipient, review the recipient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization and comply with any local requirements with respect to information to be provided to the recipient before immunization.

As with any vaccine, INTANZA™ may not protect 100% of vaccinated individuals.

Influenza virus is remarkably unpredictable in that significant antigenic changes may occur from time to time. It is known that INTANZA™ as now constituted is not effective against all possible strains of influenza virus. Protection is limited to those strains of virus from which the vaccine is prepared or against closely related strains.

Febrile or Acute Disease

Vaccination should be postponed in case of febrile or acute disease.

Immune

As with all products, epinephrine hydrochloride solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. (2) Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings including proper airway management. (2) For instructions on recognition and treatment of anaphylactic reactions see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response.

As each dose may contain traces of formaldehyde, Triton® X-100 and undetectable traces of neomycin, which are used during vaccine production, caution should be exercised when the vaccine is administered to subjects with hypersensitivity to any of these substances. (See CONTRAINDICATIONS.)

Neurologic

Immunization should be delayed in a patient with an active neurologic disorder, but should be considered when the disease process has been stabilized. (2)

Guillain-Barré syndrome (GBS) has been reported after influenza vaccination. However, it is not known whether influenza vaccination specifically might increase the risk for recurrence of GBS. Therefore, NACI and ACIP state it is prudent to avoid vaccinating persons who are known to have experienced GBS within 6 to 8 weeks after a previous influenza vaccination. (2) (3)

Special Populations

Pregnant Women

For INTANZA™, no clinical data on pregnant women are available.

In general, data from intramuscular influenza vaccinations in pregnant women do not indicate adverse fetal and maternal outcomes attributable to the vaccine. One animal study with INTANZA™ did not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development.

INTANZA™ should be given to pregnant women following an assessment of the risks and benefits in the person to be vaccinated. (2)

NACI states that influenza vaccination is recommended for all pregnant women. (3)

Nursing Women

It is not known whether INTANZA™ is excreted in human milk. Caution must be exercised when INTANZA™ is administered to a nursing mother.

For INTANZA™, no clinical data on nursing women are available.

NACI states that influenza vaccination is considered safe for breastfeeding women.

Pediatrics

INTANZA™ is not indicated for persons less than 18 years of age.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse event information is derived from clinical trials and worldwide post-marketing experience with intramuscular influenza vaccines of similar composition.

Because INTANZA™ does not contain infectious viral particles, it cannot cause influenza. Respiratory disease after vaccination represents coincidental illness unrelated to influenza vaccination.

Clinical Trial Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

The safety of INTANZA™ was evaluated in four open-label randomized clinical trials. (4) (5) (6) (7) (8) In these trials, 2,384 adults 18 to 59 years of age received a single 9 μg dose of INTANZA™, and 2,974 adults 60 years of age and over received a single 15 μg dose of INTANZA™. Table 1 presents the frequency of solicited adverse reactions reported in these clinical trials within 7 days of vaccination.

The most common reactions occurring after vaccine administration were injection site reactions. Since the immune response is activated close to the surface of the skin, as expected, apparent injection site reactions after intradermal administration were more frequent than after the control intramuscular (IM) influenza vaccine. The systemic safety profile observed after INTANZA™ was similar to the control IM influenza vaccine.

In both age groups, the most frequently reported reactions were injection site erythema, swelling and induration and the most frequently reported systemic reactions were headache, myalgia and malaise. Most reactions were mild in intensity, with the exception of severe injection site erythema, which was reported in 13.5% and 17%, respectively, in adults 18 to 59 years of age and adults 60 years of age and over. Most reactions resolved spontaneously within 1 to 3 days after onset. In some cases local redness lasted up to 7 days. (4) (5) (6) (7)

Data from clinical studies of INTANZA™ indicated that yearly repeated administration of intradermal influenza vaccination (4) (5) or alternating intramuscular and intradermal influenza vaccination (7) (9) did not alter the frequency or severity of adverse events.

Table 1: Frequency (%) of Solicited Reactions Observed in Clinical Trials in Adults Within 7 Days Following a Single Dose of Either INTANZA™ 9 µg (4) (6) or INTANZA™ 15 µg (5) (7) (8)

Solicited Reactions	INTANZA™ 9 µg 18 to 59 Years of Age N = 2,384	INTANZA™ 15 µg ≥60 Years of Age N = 2,974
Injection Site Reactions		
Erythema	85.0	71.9
Swelling	62.7	39.0
Induration	61.5	40.9
Pruritus	42.7	29.2
Pain	41.9	22.2
Ecchymosis	8.3	4.3
Systemic Reactions		
Headache	30.2	13.7
Myalgia	22.6	10.8
Malaise	17.3	9.0
Shivering	8.7	4.1
Fever (≥38.0°C)	3.8	2.4

In addition, arthralgia, asthenia (including fatigue), increased sweating, paresthesia, rash, erythema and pruritus, were reported as unsolicited adverse reactions by up to 0.6% of participants in both age groups, including isolated reports. Six cases (0.2%) of lymphadenopathy were reported in clinical trials of INTANZA™ in adults 18 to 59 years of age, as non-serious unsolicited adverse events, within 21 days after vaccine administration. (4) (5) (6) (7) One case of neuritis (brachial radiculitis) was reported as a serious adverse reaction 15 days following vaccination, among adults ≥60 years of age receiving INTANZA™ 15 µg. (7) (8)

Data from Post-Marketing Experience

There currently is no data from post-marketing experience with INTANZA™. However, the following additional systemic adverse events have been spontaneously reported during the post-marketing use of VAXIGRIP®, a trivalent inactivated influenza vaccine containing the same antigens as INTANZA™ and administered intramuscularly. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Blood and Lymphatic System Disorders

transient thrombocytopenia, lymphadenopathy

Immune System Disorders

allergic reactions: urticaria, dyspnea, angioneurotic edema, anaphylaxis including shock

Nervous System Disorders

Guillain-Barré syndrome (GBS), neuritis, neuralgia, convulsions, encephalomyelitis

Vascular Disorders

vasculitis, such as Henoch-Schonlein purpura, with transient renal involvement in certain cases

Additional Adverse Reactions

Neurological disorders temporally associated with influenza vaccination such as encephalopathy (with or without permanent neurological - motor and/or sensory - deficit and/or intellectual impairment), optic neuritis, facial paralysis, labyrinthitis and brachial plexus neuropathy have been reported. However, no cause and effect relationship has been established. (10)

Physicians, nurses and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and to the Global Pharmacovigilance Department, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

DRUG INTERACTIONS

Concomitant Vaccine Administration

No studies have been conducted regarding the concomitant administration of INTANZA™ and other vaccines.

According to NACI, inactivated vaccines usually do not interfere with the immune response to other inactivated or live vaccines (2) and influenza vaccine may be given at the same time as other vaccines, provided different sites and administration devices are used. (2) (3)

Vaccine-Drug Interactions

Immunosuppressive treatments may interfere with the development of the expected immune response. (See WARNINGS AND PRECAUTIONS.)

DOSAGE AND ADMINISTRATION

Recommended Dose

Annual influenza vaccination consists of 1 dose of INTANZA™.

Table 2: Recommended Influenza Vaccine Dosage, by Age

Age Group	Dose
18 to 59 years	0.1 mL - 9 µg/strain
60 years and over	0.1 mL - 15 µg/strain

Administration

Inspect for extraneous particulate matter and/or discolouration before use. If these conditions exist, the product should not be administered.

The vaccine should be at ambient temperature before being administered. This may be safely accomplished by holding the pre-filled micro-injection system in one's hand.

Do not shake the vaccine before use.

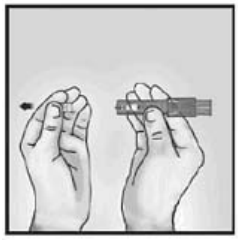
INTANZA™ is supplied in a micro-injection system for intradermal injection consisting of a pre-filled syringe with a micro-needle (1.5 mm) and a needle shielding system. The needle shielding system is designed to cover the micro-needle after use.

Administer the vaccine **intradermally**. The preferred site is in the region of the deltoid.

Clinical data suggests that re-vaccination is not required if there is liquid observed at the injection site after vaccine administration. A wheal is not required for successful vaccination.

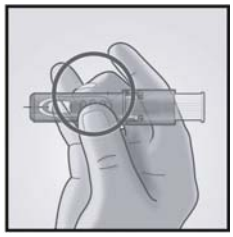
Aseptic technique must be used.

Give the patient a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. This permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.



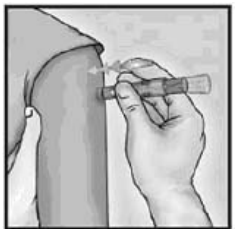
1. Remove Needle Cap

Remove the needle cap from the micro-injection system. **Do not shake the vaccine or attempt to remove the air bubble.**



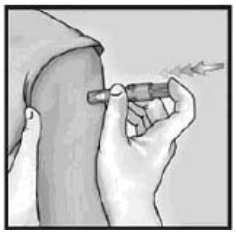
2. Hold Micro-Injection System Between Thumb and Middle Finger

Hold the system by placing the thumb and middle finger only on the finger pads, the index finger remains free. **Do not place fingers on the windows.**



3. Insert Needle Rapidly Perpendicular to the Skin

Insert the needle perpendicular to the skin, in the region of the deltoid, in a short, quick movement.



4. Inject Using the Index Finger

Once the micro-needle has been inserted, maintain a light pressure on the surface of the skin and inject using the index finger to push on the plunger. Do not aspirate.

5. Activate Needle Shield by Pushing Firmly on Plunger

Remove the needle from the skin.

Direct the needle away from you and others.

With the same hand, push very firmly with the thumb on the plunger to activate the needle shield.

You hear a click and a shield comes out to cover the needle.

Immediately dispose of the system in the nearest sharps collector.

Overdosage

Not applicable.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The following information is a summary of intradermal immune stimulation, and of the mechanism of action of influenza vaccines in general derived from published scientific and clinical research, and has not been generated specifically with INTANZA™.

Antigens administered into the dermis are rapidly captured by the dendritic cells present in high density in the skin. (11) In addition, the dermis contains a high density of lymphatic vessels and blood vessels, favouring rapid cellular and fluid exchanges and allowing direct access to the immune system. (12) Following migration to the draining lymph node, the dendritic cells, potent stimulators and modulators of the immune response, present the captured antigens to T cells, leading to T and B cell activation/expansion, thereby resulting in the induction of a sustained antigen-specific humoral and cellular immunity. (13)

Immunity to the surface antigens, especially to the haemagglutinin, reduces the likelihood of infection and lessens the severity of disease if infection occurs. Each year's influenza vaccine contains three virus strains (usually two type A and one type B) representing the influenza viruses that are believed likely to circulate in the coming winter. (1) (2) The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the strains included in each year's vaccine. (1) (2)

Protection is afforded only against those strains of virus from which the vaccine is prepared, or closely related strains. Immune response against one influenza virus type or subtype confers limited or no protection against another. Furthermore, immune response 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 incorporation of one or more new strains in each year's influenza vaccine. (14)

Pharmacodynamics

Seroprotection is expected within 2 to 3 weeks following influenza vaccination. (15)

Haemagglutination inhibiting serum antibody titres are considered appropriate surrogates of protection. (15) Comparative evaluation of the humoral immune response was the primary objective in all clinical trials with INTANZA™. The humoral immune response was assessed through the measurement of Geometric Mean Titres of HI antibodies, as well as through the evaluation of seroconversion rates, GMT increases and seroprotection rates. In clinical trials in adults 18 to 59 years of age INTANZA™ 9 µg elicited at least as high an immune response as the control IM influenza vaccine for each of the vaccine strains tested. INTANZA™ 15 µg in adults 60 years and over was demonstrated to elicit a statistically significant increase in humoral

immune response when compared to the control IM influenza vaccine for each of the vaccine strains tested. (4) (5) (6) (7) (8)

Specific sub-analyses conducted in the pivotal clinical trials of INTANZA™ in both dosages (9 µg and 15 µg) demonstrated that the absence of a wheal at the injection site or the presence of risk factors for severe influenza disease did not affect the seroprotection afforded by INTANZA™ vaccination. Participants with co-morbidity factors or with low pre-vaccination titres showed an even more pronounced increase in immune response compared to the control IM influenza vaccination. Similar sub-analyses also suggest that the presence of liquid at the injection site after vaccine administration (due to the superficial nature of the injection) does not impact the immune response to INTANZA™. (5) (6)

Pharmacokinetics

No pharmacokinetic studies have been performed.

Duration of Effect

Annual vaccination against influenza is recommended. (2)

Results from serology follow-up of adults 18 to 59 years of age immunized with INTANZA™ 9 µg in a clinical study demonstrated that seroprotection rates and GMTs above pre-vaccination levels persisted up to 12 months following vaccination. (4) The magnitude of the immune response observed within 21 days post-vaccination with INTANZA™ 15 µg in adults 60 years of age and over suggests that a similar duration of protection can be expected in this age group. (5) (7) (8)

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F). **Do not freeze**. Discard product if exposed to freezing.

Do not use after expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

INTANZA™ 9 µg and 15 µg are supplied as a sterile, colourless, opalescent suspension in pre-filled syringes with micro-injection systems.

Composition

Each 0.1 mL dose is formulated to contain:

Active Ingredients

9 µg per strain of haemagglutinin (HA) of split influenza virus, inactivated, of each strain listed below:

or

15 µg per strain of haemagglutinin (HA) of split influenza virus, inactivated, of each strain listed below:

A/California/7/2009 (H1N1)-like strain, A/Perth/16/2009 (H3N2)-like strain and B/Brisbane/60/2008.

Other Ingredients

Buffer solution (up to 0.1 mL) containing:

sodium chloride	0.8 mg
potassium chloride	0.02 mg
disodium phosphate dihydrate	0.115 mg
potassium dihydrogen phosphate	0.02 mg

Manufacturing process residuals: neomycin, formaldehyde, ovalbumin and Triton® X-100 may be present in trace amounts.

Packaging

INTANZA™ is supplied in single-dose pre-filled syringes with micro-injection systems equipped with a needle shield to be activated post-administration. The syringes are made of Ph. Eur. Type I glass. The container closure system for INTANZA™ does not contain latex (natural rubber).

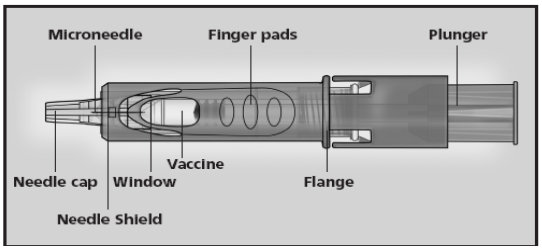
INTANZA™ is available in a package of:

1 x 0.1 mL pre-filled Micro-Injection System

10 x 0.1 mL pre-filled Micro-Injection Systems

Not all pack sizes may be marketed.

Micro-Injection System



Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business Hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of May 2010.

Manufactured by:
Sanofi Pasteur SA
Lyon, France

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R0-0510 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Influenza Vaccine (Split Virion, Inactivated)

Product Characteristics

INTANZA™ is a sterile, uniform, colourless and opalescent suspension prepared from influenza viruses cultivated in embryonated hens' eggs. Each of the strains is separately inoculated into the allantoic cavity of chicken embryos with neomycin solution equivalent to 0.5 mg per egg. Following incubation, the allantoic fluid is collected and clarified and the viruses are concentrated, then purified by zonal centrifugation using a sucrose density gradient. Subsequent stages consist of treatment with Triton® X-100 to obtain split antigens, then inactivation using formaldehyde solution and concentrated. The final vaccine is obtained by mixing the three strains in a buffer solution.

CLINICAL TRIALS

Study Demographics and Trial Design

Four clinical trials were conducted in Europe, Australia and New Zealand (see Table 3) with INTANZA™ formulated using the strains A/H1N1, A/H3N2 and B recommended by WHO for the respective influenza season.

Table 3: Summary of Demographics and Study Design

Study	Study Design	Dosage and Route of Administration	Study Participants N = number*		Mean Age Range (Years)	Gender N = number* Males/Females
			Randomized	Immuno-genicity†		
GID15	Randomized, controlled, open-label, comparative trial of INTANZA™ 9 µg compared to IM influenza vaccine 15 µg.	9 µg/0.1 mL, ID 15 µg/0.5 mL, IM	N = 588 N = 390	N = 381 N = 379	40.2 (18:1, 58:0) 40.2 (18:4, 58:0)	N = 141/240 N = 138/241
GID23	Randomized, controlled, open-label, comparative trial of INTANZA™ 9 µg compared to IM influenza vaccine 15 µg.	9 µg/0.1 mL, ID 15 µg/0.5 mL, IM	N = 1,803 N = 452	N = 1,255 N = 421	43.1 (18:1, 60:0) 42.0 (18:1, 60:0)	N = 500/755 N = 171/250
GID16	Randomized, controlled, open-label, comparative trial of INTANZA™ 15 µg and 21 µg compared to IM influenza vaccine 15 µg.	15 µg/0.1 mL, ID 15 µg/0.5 mL, IM	N = 370 N = 368	N = 359 N = 358	70.9 (60:1, 84.8) 71.0 (60.0:85.7)	N = 155/204 N = 170/188
GID17	Randomized, controlled, open-label, comparative trial of INTANZA 15 µg compared to IM influenza vaccine 15 µg.	15 µg/0.1 mL, ID 15 µg/0.5 mL, IM	N = 2,618 N = 1,089	N = 2,558 N = 1,068	70.7 (60.0:93.7) 70.9 (60.1:94.6)	N = 1,186/1,418 N = 495/586

* Number of participants in each treatment group

† Per protocol population; immunogenicity tested in subset only for GID15 and GID23.

IMMUNOGENICITY

Criteria for evaluation of the immune response

As is the case with influenza infections, the humoral immune response to influenza vaccination involves the production of specific haemagglutination-inhibiting immunoglobulins M and G, which both have the ability to inhibit haemagglutination. Therefore, Haemagglutination Inhibition (HI) titres are considered appropriate surrogates of protection against influenza infection and disease. (15) (16) (17) Therefore, in all clinical trials of INTANZA™, analyses of HI GMTs constituted primary objectives for evaluation of the immune response. HI GMTs elicited by INTANZA™ were compared to those elicited by the control IM influenza vaccine. GMT analyses were conducted on the Per Protocol population. In addition, the humoral immune response to

INTANZA™ vaccination was evaluated through the criteria for immunogenicity of influenza vaccines defined by the European Medicines Evaluation Agency (EMEA). (18) (See Table 4.) The populations for these statistical analyses included all participants with pre- and post-vaccination serology results.

Table 4: EMEA Criteria for Immunogenicity of Influenza Vaccines as Defined in the Note for Guidance on the "Harmonization Requirements for Influenza Vaccines"

Age (years)	18 to 59	60 and over
Seroconversion rate* or significant increase† of titre 21 days after vaccination	>40%	>30%
Mean geometric‡ increase between pre- and post-vaccination	>2.5	>2
Percentage of seroprotected§ subjects 21 days after vaccination	>70%	>60%

* For subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post-vaccination titre ≥40 (1/dil) (HI Technique).

† For subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥4-fold increase from pre- to post-vaccination titre (HI Technique).

‡ Geometric mean of individual ratios (post-/pre-vaccination titres).

§ Proportion of subjects achieving a post-vaccination titre ≥40 (1/dil).

Immunogenicity of INTANZA™ 9 µg in adults 18 to 59 years of age

The immunogenicity of INTANZA™ 9 µg in adults 18 to 59 years of age was evaluated 21 days after vaccination in two pivotal studies. (See Table 5.) (4) (6) In both studies and for each strain included in the trivalent formulation tested, INTANZA™ 9 µg was shown to be at least as immunogenic as the control IM influenza vaccine and the immune response to INTANZA™ 9 µg met all of the EMEA-defined immunogenicity criteria.

Table 5: Antibody Response in Adults 18 to 59 Years of Age 21 Days After Vaccination with INTANZA™ 9 µg

9 µg ID	GID15		GID23	
	9 µg ID	**15 µg IM**	**9 µg ID**	**15 µg IM**
	N = 381	N = 379	N = 1,255	N = 421
A/H1N1 Strain				
GMT (95% CI)	249* (216; 287)	199 (170; 232)	182* (168; 197)	187 (162; 216)
Non-inferiority analysis $Log_{10}(GMT_{ID})$-$Log_{10}(GMT_{IM})$	0.098* (0.006; 0.189)		-0.013* (-0.084; 0.059)	
Post-vaccination seroprotection rate % (95% CI)	92.4 (89.3; 94.9)	88.8 (85.3; 91.8)	87.2 (85.2; 89.0)	86.2 (82.6; 89.3)
GMT Ratios (95% CI)	16.2 (13.7; 19.2)	13.8 (11.6; 16.4)	9.17 (8.33; 10.1)	9.71 (8.19; 11.5)
Seroconversion or significant increase rate % (95% CI)	74.3 (69.7; 78.7)	70.4 (65.6; 74.9)	57.5 (54.7; 60.2)	56.4 (51.6; 61.1)
A/H3N2 Strain				
GMT (95% CI)	828* (738; 928)	571 (502; 649)	278* (257; 301)	274 (244; 309)
Non-inferiority analysis $Log_{10}(GMT_{ID})$-$Log_{10}(GMT_{IM})$	0.162* (0.087; 0.236)		0.006* (-0.059; 0.072)	
Post-vaccination seroprotection rate % (95% CI)	99.7 (98.6; 100.0)	98.7 (97.0; 99.6)	93.5 (92.0; 94.8)	95.4 (93.0; 97.2)
GMT Ratios (95% CI)	28.2 (23.7; 33.5)	20.7 (17.5; 24.4)	11.5 (10.4; 12.7)	11.2 (9.58; 13.1)
Seroconversion or significant increase rate % (95% CI)	85.1 (81.2; 88.5)	79.2 (74.8; 83.1)	66.5 (63.8; 69.0)	69.3 (64.7; 73.6)
B Strain				
GMT (95% CI)	144* (129; 161)	124 (110; 139)	68.3* (64.1; 72.7)	69.8 (62.7; 77.8)
Non-inferiority analysis $Log_{10}(GMT_{ID})$-$Log_{10}(GMT_{IM})$	0.067* (-0.003; 0.136)		-0.010* (-0.064; 0.044)	
Post-vaccination seroprotection rate % (95% CI)	90.6 (87.2; 93.3)	85.5 (81.5; 88.8)	72.9 (70.4; 75.3)	74.8 (70.4; 78.8)
GMT Ratios (95% CI)	12.1 (10.5; 13.8)	10.84 (9.56; 12.29)	6.39 (5.96; 6.84)	6.63 (5.90; 7.46)
Seroconversion or significant increase rate % (95% CI)	76.4 (71.9; 80.6)	73.5 (68.8; 77.8)	56.7 (54.0; 59.4)	60.8 (56.0; 65.4)

* Predefined criteria met for non-inferiority of INTANZA™ 9 µg compared to the control IM influenza. The non inferiority criterion in studies GID15 and GID23 was met if, for all three strains, the lower bound of the 95% CI of the difference $Log_{10}(GMT_{ID})$-$Log_{10}(GMT_{IM})$ was > -0.176 (equivalent to ratio GMT_{IM}/GMT_{ID} < 1.5).

The effect of the presence or absence of a wheal after intradermal injection was evaluated. In one study, approximately one-half of all participants who received INTANZA™ 9 µg presented a wheal at injection site. In those without a wheal, all EMEA criteria were met and the immune response was not inferior to that observed after vaccination with the control IM influenza vaccine. These data confirm that with the micro-injection system, a wheal is not required for successful immunization.

Overall, approximately 5% of all participants in both studies had the presence of liquid at the injection site after vaccine administration. In one study, participants presenting with the presence of liquid at the injection site had a slightly lower immune response with respect to those without the presence of liquid at the injection site. However, and despite the small sample size (N = 59 analyzable), all three EMEA criteria were fulfilled for each strain for participants with the presence of liquid at the injection site, except the seroprotection rate for the B strain. These data suggest that the presence of liquid at the injection site does not significantly impact the immune response and, therefore, does not warrant re-vaccination.

Antibody persistence one year after vaccination was evaluated in study GID15. Blood samples were taken 3, 6 and 12 months after vaccination, in addition to the Day 21 sample. Approximately 350 participants having received either INTANZA™ 9 µg or the control IM influenza vaccine were followed to Month 12. Seroprotection rates and GMTs for participants administered either with INTANZA™ 9 µg or the control IM vaccine decreased similarly with time after vaccination, as shown by the 95% CIs which largely overlapped for each time point. Seroprotection rates and GMTs above pre-vaccination levels were seen for all strains at all post-vaccination time points tested.

Immunogenicity of INTANZA™ 15 µg in adults 60 years of age and over

The immunogenicity of INTANZA™ 15 µg in adults 60 years of age and over was evaluated 21 days after vaccination in two key studies. (See Table 6.) (5) (7) (8) Protocol-defined criteria for non-inferiority and superiority of INTANZA™ 15 µg compared to the control IM influenza vaccine were met in each trial and for each strain included in the formulations tested. The difference in seroprotection rates afforded by INTANZA™ 15 µg compared to the control IM influenza vaccine ranged from 4.7% to 10.8%, across the two trials. The EMEA-defined immunogenicity criteria were also met for each strain following vaccination with the INTANZA™ 15 µg, with the exception of the seroprotection rate for the B strain in study GID17. This criterion was also not met following vaccination with the control IM influenza vaccine.

Table 6: Antibody Response in Adults 60 Years of Age and Over 21 Days After Vaccination with INTANZA™ 15 µg

15 µg ID	GID16		GID17	
	15 µg ID	**15 µg IM**	**15 µg ID**	**15 µg IM**
	N = 365	N = 363	N = 2,595	N = 1,077
A/H1N1 Strain				
GMT (95% CI)	86.7* (76.7; 98.1)	56.9 (51.1; 63.4)	81.9* (78.2; 85.8)	69.1 (64.1; 74.4)
Non-inferiority analysis $Log_{10}(GMT_{ID})$-$Log_{10}(GMT_{IM})$	0.181* (0.109; 0.252)		0.076* (0.038; 0.114)	
Post-vaccination seroprotection rate % (95% CI)	77.5 (72.9; 81.7)	72.2 (67.3; 76.7)	77.0 (75.3; 78.6)	71.2 (68.4; 73.9)
GMT Ratios (95% CI)	3.73 (3.28; 4.24)	2.37 (2.13; 2.63)	3.97 (3.77; 4.18)	3.19 (2.94; 3.45)
Seroconversion or significant increase rate % (95% CI)	41.3 (36.2; 46.6)	22.3 (18.1; 26.9)	38.7 (36.8; 40.6)	30.0 (27.3; 32.9)
A/H3N2 Strain				
GMT (95% CI)	400* (354; 452)	235 (205; 268)	298* (282; 315)	181 (167; 197)
Non-inferiority analysis $Log_{10}(GMT_{ID})$-$Log_{10}(GMT_{IM})$	0.231* (0.152; 0.311)		0.215* (0.171; 0.259)	
Post-vaccination seroprotection rate % (95% CI)	98.1 (96.1; 99.2)	93.4 (90.3; 95.7)	93.3 (92.3; 94.3)	87.8 (85.7; 89.7)
GMT Ratios (95% CI)	4.14 (3.56; 4.83)	2.68 (2.36; 3.04)	8.19 (7.68; 8.74)	5.35 (4.87; 5.88)
Seroconversion or significant increase rate % (95% CI)	42.3 (36.2; 46.6)	27.2 (22.7; 32.1)	61.3 (59.3; 63.1)	46.9 (43.9; 49.9)
B Strain				
GMT (95% CI)	100* (89.6; 112)	67.7 (60.6. 75.7)	39.9* (38.2; 41.6)	34.9 (32.7; 37.3)
Non-inferiority analysis $Log_{10}(GMT_{ID})$-$Log_{10}(GMT_{IM})$	0.174* (0.106; 0.242)		0.060* (0.026; 0.094)	
Post-vaccination seroprotection rate % (95% CI)	84.7 (80.6; 88.2)	73.9 (69.2; 78.4)	55.7 (53.7; 57.6)	49.1 (46.0; 52.1)
GMT Ratios (95% CI)	3.65 (3.26; 4.10)	2.69 (2.43; 2.98)	3.61 (3.47; 3.76)	3.04 (2.85; 3.24)
Seroconversion or significant increase rate % (95% CI)	43.1 (39.0; 48.4)	29.9 (25.2; 34.8)	36.4 (34.5; 38.3)	30.7 (28.0; 33.6)

* Predefined criteria met for non-inferiority of INTANZA™ 15 µg compared to the control IM influenza. The non inferiority criterion in studies GID16 and GID17 was met if, for all three strains, the lower bound of the 95% CI of the difference $Log_{10}(GMT_{ID})$-$Log_{10}(GMT_{IM})$ was > -0.176 (equivalent to ratio $GMT_{IM}/GMT_{ID} < 1.5$).

In study GID17, among the substantial proportion of participants who were not seroprotected before vaccination, post-vaccination seroprotection rates were higher for INTANZA™ recipients than for recipients of the control IM influenza vaccine. The differences in seroprotection rates ranged from 7.34% to 9.65%. Participants with high-risk medical conditions had a similar or higher degree of seroprotection after INTANZA™ 15 µg vaccination as those participants who were not at high risk, for all three strains. Importantly, seroprotection rates remained higher for participants administered INTANZA™ 15 µg compared to those administered the control IM influenza vaccine.

Further sub-analyses were conducted in study GID17 to evaluate the effect of the presence of liquid at the injection site after vaccine administration and of the presence, or absence, of a wheal on the immune response to INTANZA™ 15 µg. The presence of liquid at the injection site after vaccine administration was reported for 2.5% of the participants administered INTANZA™ 15 µg, for a total of 65 participants. There was no relevant difference between participants presenting with the presence of liquid at the injection site and those without the presence of liquid at the injection site in terms of post-vaccination GMTs. Post-vaccination GMTs and seroprotection rates observed in participants presenting a wheal were similar to those observed in participants without a wheal for the three strains. These data further confirm that a wheal is not required for correct immunization when the micro-injection system is used.

SAFETY

Pooled data from the four trials GID15, GID23, GID16 and GID17 represent a total of 2,384 participants who received INTANZA™ 9 µg and 2,974 participants who received INTANZA™ 15 µg. Comparison is made with 843 and 1,458 participants, respectively, who received the control IM influenza vaccine. (See Table 7.)

A higher incidence of injection site reactions following INTANZA™ vaccination compared to IM injection was seen in the four trials. Injection site erythema, swelling, induration were more frequent and more extensive in participants vaccinated with INTANZA™ compared to the IM influenza vaccine; pruritis was also more frequently reported following INTANZA™ vaccination. The majority of the injection site reactions began the day following vaccination, lasted up to 3 days and resolved spontaneously. With the exception of injection site erythema, the majority of injection site reactions were mild.

Data from these four studies also confirm that the incidences of systemic reactions were similar following INTANZA™ compared to IM influenza vaccine. The incidence of moderate or severe systemic reactions was not higher after vaccination with INTANZA™ (non-superiority analyzed according to pre-defined criteria) in either study GID17 or study GID23.

Table 7: Injection Site and Systemic Solicited Reactions After Vaccination with either INTANZA™ 9 µg in Adults 18 to 59 Years of Age, INTANZA™ 15 µg in Adults 60 Years of Age and Over, or the Control IM influenza vaccine in Studies GID15, GID23, GID16 and GID17

Symptom	Grade	Adults 18 to 59 Years of Age		Adults 60 Years of Age and Over	
		9 µg ID N = 2,384 %	15 µg IM N = 843 %	15 µg ID N = 2,974 %	15 µg IM N = 1,458 %
Injection Site Reactions (Evaluation from Day 0 to Day 8 After Vaccination					
Injection Site Pain	Any	41.9	44.0	22.2	17.1
	Severe	0.1	0.1	0.2	0.0
Injection Site Erythema	Any	85.0	19.0	71.9	16.1
	Severe	17.0	2.9	13.2	2.1
Injection Site Swelling	Any	62.7	14.9	39.0	9.7
	Severe	6.3	1.6	3.9	1.1
Injection Site Induration	Any	61.5	19.9	40.9	12.6
	Severe	4.4	1.1	2.2	0.9
Injection Site Ecchymosis	Any	8.3	6.5	4.3	4.2
	Severe	0.5	0.4	0.4	0.2
Injection Site Pruritus	Any	42.7	9.1	29.2	6.8
	Severe	0.4	0.1	0.3	0.1
Systemic Reactions (Evaluation from Day 0 to Day 21 After Vaccination)					
Fever	Any	3.8	3.5	2.4	3.5
	Moderate/Severe	0.8	0.7	0.5	0.6
Headache	Any	30.2	30.1	13.7	13.9
	Moderate/Severe	8.1	8.5	2.3	2.2
Malaise	Any	17.3	18.4	9.0	8.4
	Moderate/Severe	5.4	6.0	2.0	2.3
Myalgia	Any	22.6	29.5	10.8	11.2
	Moderate/Severe	4.7	5.0	2.2	2.8
Shivering	Any	8.7	8.0	4.1	4.8
	Moderate/Severe	2.0	1.7	0.7	0.6

Injection site pain was evaluated as an exploratory objective in studies GID17 and GID23 using two different questionnaires - a Verbal Rating Scale (VRS) and a Patient Reported Vaccination Outcome questionnaire developed according to guidelines published by the European Regulatory Issues on Quality of Life Assessment Group (ERIQA). (19) (20) Most participants (80.3% in adults 18- 59 years of age with INTANZA™ 9 µg, to 89.1% in older adults ≥ 60 years of age with INTANZA™ 15 µg) reported that they felt no pain or hardly any pain upon ID delivery. Twenty-one days after vaccination, 96% of adults 18 to 59 years of age and 97% of adults 60 years of age and over reported that they were satisfied with the ID Micro-Injection System and that the pain at the injection site was "totally acceptable" or "very acceptable".

TOXICOLOGY

Pre-clinical toxicology program

The nonclinical safety evaluation of the trivalent influenza vaccine administered via the intradermal (ID) route consisted of two repeated dose toxicity studies, two local tolerance studies (single or repeated dose) and a developmental toxicity study. (Table 8)

Table 8: INTANZA™ Pre-clinical Toxicology Program

Study design	Route of administration	Species	Products administered
Repeated dose toxicity **Four injections** (Days 0, 14, 28, 42) **Observation period:** 44 or 56 days	ID or IM	Rabbit	Intradermal influenza vaccine: - 6 µg hemagglutinin (HA)/influenza strain/0.1 mL - 9 µg HA/influenza strain/0.1 mL Intramuscular influenza vaccine: - 15 µg HA/influenza strain/0.5 mL
Repeated dose toxicity **Three injections** (Days 0, 14, 28) **Observation period:** 30 or 42 days	ID or IM	Rabbit	Intradermal influenza vaccine: - 15 µg HA/influenza strain/0.1 mL - 21 µg HA/influenza strain/0.1 mL Intramuscular influenza vaccine: - 15 µg HA/influenza strain/0.5 mL
Local tolerance **Single injection** (Day 0) **Observation period:** 3 or 14 days	ID	Rabbit	Intradermal influenza vaccine: - 9 µg HA/influenza strain/0.1 mL
Local tolerance **Three injections** (Days 0, 14, 28) **Observation period:** 31 or 42 days	ID	Rabbit	Intradermal influenza vaccine: - 9 µg HA/influenza strain/0.1 mL

Study design	Route of administration	Species	Products administered
Developmental toxicity **Four injections:** 24 and 10 days before mating, day 6 or 12 of gestation and day 27 of gestation **Observation period:** 29 days post-coitum or 35 days post-partum	ID	Rabbit	Intradermal influenza vaccine: - 9 µg HA/influenza strain/0.1 mL

Systemic toxicity

In repeated dose studies, there were no premature deaths or adverse clinical signs, no adverse effects on body weight, food consumption and ophthalmology or organ weights. A slight decrease in white blood cells counts was observed in females after repeated injections of the highest dose tested (21 µg HA/influenza strain) via ID route, which could be related to the local inflammatory response to the vaccine and to the mobilization of the immune cells to the lymphoid organs. This hematological change could be linked to microscopic findings observed in the spleen and lymph nodes (increased cellularity) which were considered to be related to the biological activity of the vaccine (immune stimulation) and were of no toxicological significance.

Local tolerance

The main effects observed in all the studies were local reactions consisting of erythema and edema, which persisted for one to two weeks. In all the local tolerance studies and repeated dose toxicity studies conducted with this vaccine, the severity of injections site reactions ranged from very mild to moderate erythema and was associated with mild to severe edema. The severity and incidence of these local effects increased with the number of injections and there was a slight dose-related effect for edema. Generally, the peak of reactions (maximum mean scores) was observed earlier after each subsequent injection compared to the first, and was of shorter duration. All the reactions seen at the ID injected sites were associated histologically with inflammatory responses (dermal mixed inflammation) that were dose-related and that partially recovered after two weeks.

When alternate routes (ID or IM) were evaluated, no specific findings were observed except that a priming vaccination via IM route led to increased local reactions after a subsequent ID injection. Rare resurgence of reactions was observed at previous vaccination sites, in two cases out of 136 rabbits (all studies combined) treated with repeated doses. The localization of these reactions (between the initial injection site and the draining lymph nodes) suggested that they were likely to be due to local persistence of the antigen in the skin during the two weeks that separated the injections and to the recruitment of local memory cells following the subsequent injection.

The reactions observed at the ID sites were expected as they reflected the immune response triggered after repeated exposure to the vaccine by the ID route (multiple injections every two weeks). Indeed, the immune response is activated close to the surface of the skin and the effects are more apparent than with the IM route.

Developmental toxicity

Repeated treatments of female rabbits with the intradermal influenza vaccine at 9 µg HA/influenza strain had no effects on the mating performance and fertility. There was no indication of maternal systemic toxicity induced during the gestation and lactation periods, no effect on pre and post natal development and no indication of a teratogenic potential. Treatment-related local reactions were mainly characterized by mild to severe edema and erythema.

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Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business Hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.
Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of May 2010.

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Sanofi Pasteur SA
Lyon, France

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R0-0510 Canada

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

INTANZA™

Influenza Vaccine (Split Virion, Inactivated)

This leaflet is part III of a three-part "Product Monograph" published when INTANZA™ was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about INTANZA™. Contact your doctor, nurse or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

INTANZA™ is a vaccine that is used to help prevent influenza. Influenza (or flu) is an infection caused by the influenza virus. This vaccine may be given to adults 18 years of age and over.

The majority of individuals who are vaccinated with INTANZA™ will produce enough antibodies to help protect them against this disease. However, as with all vaccines, 100% protection cannot be guaranteed.

What it does:

INTANZA™ causes the body to produce its own natural protection against influenza virus. After you receive the vaccine, the body begins to make substances called antibodies. Antibodies help the body to fight disease. If a vaccinated person comes into contact with one of the germs that cause this disease, the body is usually ready to destroy it.

When it should not be used:

- Do not give INTANZA™ to anyone who has ever had an allergic reaction to:
  - egg or egg products
  - chicken protein
  - any component of INTANZA™ or its container

What the medicinal ingredient is:

Each 0.1 mL dose of INTANZA™ contains 9 µg or 15 µg of haemagglutinin antigens (HA) of split influenza virus*, inactivated, equivalent to the strains listed below:

A/California/7/2009 (H1N1)-like strain, A/Perth/16/2009 (H3N2)-like strain and B/Brisbane/60/2008.

What the important non-medicinal ingredients are:

Manufacturing process residuals: neomycin, formaldehyde, ovalbumin and Triton X®100 may be present in trace amounts.

What dosage forms it comes in:

INTANZA™ is a liquid vaccine that is injected just under the surface of the skin. A single dose is 0.1 mL.

WARNINGS AND PRECAUTIONS

INTANZA™ will only protect against the strains of flu virus contained in the vaccine or those that are closely related.

INTANZA™ will not protect against any other strains of flu virus.

If you have any of the following conditions, talk to your doctor, nurse or pharmacist BEFORE you use INTANZA™:

- **A high fever or serious illness.** Wait until you are better to receive the vaccination.
- **Allergy to any component of the vaccine or the container.**
- **An evolving disease of the nervous system.** Your doctor will advise of a more appropriate time to receive the vaccination.
- **A history of Guillain-Barré syndrome (GBS) within 6 to 8 weeks of a previous influenza vaccination.**
- **Diseases of the immune system or are taking a medical treatment that affects the immune system.** The vaccine may provide you with a lower level of protection than it does for people with healthy immune systems.

INTERACTIONS WITH THIS VACCINE

No studies have been conducted on the administration of INTANZA™ at the same time as other vaccines.

PROPER USE OF THIS VACCINE

Usual Dose

For persons 18 to 59 years of age 9 µg HA/0.1 mL.

For persons 60 years of age and over 15 µg HA/0.1 mL.

The vaccination should be given just under the skin (intradermally) near the shoulder (deltoid) region.

Overdose

Not applicable to this vaccine.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A vaccine, like any medicine, may cause side effects. The risk of INTANZA™ causing serious harm is extremely small. The small risks associated with INTANZA™ are much less than the risks associated with getting the disease against which it protects.

The flu vaccine cannot cause influenza because it does not contain any live virus. As the vaccine is given just under the surface of the skin, the most common side effects are located where you received the injection and include redness, swelling, a lump, itching and soreness. You might also notice headache, muscle aches and tiredness. Usually, side effects are mild and may last one to three days.

Severe allergic reactions to the flu shots are very rare. A very rare but possible side effect of influenza vaccination is Guillain-Barré syndrome (GBS). This is an autoimmune disease that attacks the nervous system. GBS causes weakness and abnormal sensations. Most patients recover fully.

Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well after receiving INTANZA™.

This is not a complete list of side effects. For any unexpected effects after taking INTANZA™, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store the vaccine in a refrigerator at 2° to 8°C (35° to 46°F). **Do not freeze**. Throw the product away if it has been exposed to freezing.

Do not use after expiration date.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected adverse events following vaccination.

If you suspect you or your child has had a serious or unexpected event following receipt of a vaccine you may notify the Public Health Agency of Canada:

by toll-free telephone: 1-866-844-0018
by toll-free fax: 1-866-844-5931
web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php
by regular mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, ON K1A 0K9
A/L 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. **The Public Health Agency of Canada does not provide medical advice**.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.sanofipasteur.ca

You may also contact the vaccine producer, Sanofi Pasteur Limited for more information. Telephone: 1-888-621-1146 (no charge) or 416-667-2779 (Toronto area).

Business Hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

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