

Australian Product Information

NAME OF THE MEDICINE

INTANZA 9µg/strain/0.1 mL suspension for injection in pre-filled syringe with a Micro- Injection System. Influenza vaccine (split virion, inactivated).

DESCRIPTION

Active ingredients:

Split Influenza virus*, inactivated, containing antigens equivalent to the following strains:

- A/California/7/2009 (H1N1) like strain (A/California/7/2009 (NYMC X-179A) 9 micrograms HA**
- A/Perth/16/2009 (H3N2) like strain (A/Wisconsin/15/2009 (NYMC X-183) 9 micrograms HA**
- B/Brisbane/60/2008 like strain (B/Brisbane/60/2008) 9 micrograms HA**

Per 0.1 mL dose

* propagated in fertilised hens' eggs from healthy chicken flocks

** haemagglutinin

The vaccine complies with the TGA recommendations (Southern Hemisphere) for the 2010 season.

Excipients:

Buffer solution:

- Sodium chloride
- Potassium chloride
- Sodium phosphate - dibasic dihydrate
- Potassium phosphate - monobasic
- Water for injections

No adjuvant or antimicrobial preservative is added. The vaccine does not contain more than 0.05 microgram of ovalbumin per dose. In each dose the vaccine may contain traces of octoxinol 9 (\leq 150 microgram), formaldehyde (\leq 0.6 microgram) and neomycin (\leq 0.05 picogram).

The vaccine is a colourless and opalescent suspension for injection in pre-filled syringe with a Micro-Injection System.

PHARMACOLOGY

Mechanism of action

Antigen administered into the dermis is rapidly captured by dendritic cells present at high density in the skin. Following migration to the draining lymph node, the dendritic cells present the captured antigen to T cells, which lead to T and B cell activation/expansion, thereby resulting in the induction of a sustained antigen-specific cellular and humoral immunity. Antibody concentrations in serum considered protective are generally obtained within 2 to 3 weeks. The persistence of post-vaccination immunity related to the vaccine strains is 6-12 months as shown by a study performed during the clinical development of this vaccine. Protection is limited to the influenza strains from which the vaccine is prepared or to closely related strains.

CLINICAL TRIALS

Immunogenicity

INTANZA 9µg is as immunogenic as a trivalent inactivated influenza vaccine administered by intramuscular route for each of the 3 influenza strains in subjects 18 to 59 years of age.

In a randomised comparative phase III trial, 1796 subjects 18 to 59 years of age received 0.1 mL of INTANZA 9µg by the intradermal route and 453 subjects from 18 to 59 years of age received 0.5 mL of a trivalent inactivated influenza vaccine administered by the intramuscular route. In this comparative trial the seroprotection rate*, seroconversion or significant increase rate** and the geometric mean titre ratio (GMTR) for anti-HA antibody (measured by HI) were assessed according to predefined criteria.

Data were as follows (values in brackets show the 95% confidence intervals):

	Intradermal 9µg			Comparator-Intramuscular 15µg		
	A/H1N1	A/H3N2	B	A/H1N1	A/H3N2	B
	A/New Caledonia/ 20/09	A/Wisconsin/ 67/2005	B/Malaysia/ 2506/2004	A/New Caledonia/20/09	A/Wisconsin/ 67/2005	B/Malaysia/ 2506/2004
	N=1,296	N=1,297	N=1,294	N = 436	N = 436	N = 436
Geometric mean of titers (1/dil)	181 (168 ; 197)	277 (257 ; 299)	67.7 (63.7 ; 72.0)	186 (161 ; 214)	271 (241 ; 306)	68.9 (61.9 ; 76.8)
Seroprotection rate (%) *	87.2 (85.2 ; 89.0)	93.5 (92.0 ; 94.8)	72.9 (70.4 ; 75.3)	86.2 (82.6 ; 89.3)	95.4 (93.0 ; 97.2)	74.8 (70.4 ; 78.8)
Seroconversion or significant increase rate (%) **	57.5 (54.7 ; 60.2)	66.5 (63.8 ; 69.0)	56.7 (54.0 ; 59.4)	56.4 (51.6 ; 61.1)	69.3 (64.7 ; 73.6)	60.8 (56.0 ; 65.4)
Geometric mean of titer ratio (GMTR)	9.17 (8.33 ; 10.1)	11.5 (10.4 ; 12.7)	6.39 (5.96 ; 6.84)	9.71 (8.19 ; 11.5)	11.2 (9.58 ; 13.1)	6.63 (5.90 ; 7.46)

* Seroprotection = HI titre \geq 40

** Seroconversion = negative pre-vaccination HI titre and post vaccination HI titre \geq 40,

Significant increase = positive pre-vaccination HI titre and at least a 4-fold increase in postvaccination HI titre

GMTR: Geometric mean titre ratio of individual (post-/pre-vaccination titre)

After vaccination, the seroprotection rates of INTANZA 9µg were 87.2%, 93.5% and 72.9% with the A/H1N1, A/H3N2 and B strains respectively. These results were comparable with those observed with a trivalent inactivated influenza vaccine administered by the intramuscular route.

INTANZA 9µg, 21 days after the vaccination, showed immune responses with geometric mean titres at 181, 277 and 67.7 for the A/H1N1, A/H3N2 and B strains respectively. The immune responses were statistically non-inferior to a trivalent inactivated influenza vaccine administered by intramuscular route for each of the three influenza strains.

INDICATIONS

INTANZA 9µg is indicated for prophylaxis of influenza in adults from 18 to 59 years of age.

The use of INTANZA 9µg in Australia should be based on the NHMRC recommendations for influenza vaccination as published in the current Australian Immunisation Handbook.

CONTRAINDICATIONS

INTANZA 9µg should not be given to persons with known anaphylactic hypersensitivity reactions to egg proteins (eggs or egg products), chicken proteins, or other component of the vaccine including traces (formaldehyde, octoxinol 9 (Triton X-100) and neomycin).

Immunisation shall be postponed in subjects with febrile illness or acute infection.

PRECAUTIONS

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Patients with a history of Guillain-Barré Syndrome (GBS) with an onset related in time to influenza vaccination may be at increased risk of again developing GBS if given influenza vaccine. While this risk should be weighed against the benefits to the individual patient of influenza vaccination, it should seem prudent to avoid subsequent influenza vaccination in this group. Because patients with a history of GBS have an increased likelihood of again developing the syndrome, the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in individuals with no history of GBS.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient. Nevertheless, vaccination of individuals with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited.

USE IN CHILDREN

INTANZA 9µg is not recommended for use in children and adolescents below 18 years due to insufficient data on safety and efficacy

USE IN PREGNANCY (CATEGORY B1)

One developmental toxicity study conducted in rabbits with INTANZA 9µg did not show any effects on female fertility, pregnancy, embryo-fetal development and early postnatal development.

For INTANZA 9µg no clinical data on exposed pregnancies are available. Postmarketing data on the use of trivalent vaccines administered intramuscularly in pregnant women are limited. They do not indicate that adverse fetal and maternal outcomes were attributable to these vaccines.

INTANZA 9µg should be given to pregnant women only if clearly needed and following an assessment of the risks and benefit.

USE IN LACTATION

It is not known whether INTANZA 9µg is excreted in human milk. Caution must be exercised when INTANZA 9µg is administered to a nursing mother. In rabbits, after injection of INTANZA 9µg during pregnancy, antibodies against the 3 influenza strains were detected in dams and pups. These antibodies had no effects on pup development assessed during lactation (see also Use in Pregnancy).

CARCINOGENICITY AND GENOTOXICITY

INTANZA has not been tested for the carcinogenic or genotoxic potential.

INTERACTIONS

INTANZA 9µg may be given at the same time as other vaccines. Immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

Studies have not been conducted to assess administration of other vaccines concomitantly with INTANZA 9µg.

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the false-positive ELISA test results. The transient false positive reactions could be due to the IgM response by the vaccine.

EFFECT ON ABILITY TO DRIVE

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

ADVERSE EFFECTS

Clinical Trials Experience

The safety of INTANZA 9µg has been assessed in 2 open-label randomised clinical trials in which 2384 vaccinees received an injection of INTANZA 9µg. The most common reactions occurring after a first vaccine administration were local reactions at the injection site. As the immune response is activated close to the surface of the skin, apparent local reactions are anticipated to be frequent. Most reactions resolved spontaneously within 1 to 3 days after onset. In some cases, local erythema lasted up to 7 days.

The impact of local reactions on subjects' quality of life was measured by using a Patient Reported Outcome (PRO) instrument developed according to ERIQA (European Regulatory Issues on Quality of Life Assessment Group) recommendations. Amongst approximately 2100 subjects vaccinated with INTANZA 9µg and who answered the question, 96% considered these local reactions 'totally acceptable' or 'very acceptable'. The impact of local reactions on subjects' daily quality of life (sleep or arm movement) was very low, with minimal bother.

After repetitive yearly injections of INTANZA 9µg the safety profile was similar to the first injection of INTANZA 9µg.

Reactions are ranked within each system organ class, under headings of frequency, using the following convention [Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1\ 000$, $< 1/100$); rare ($\geq 1/10\ 000$, $< 1/1\ 000$); very rare ($< 1/10\ 000$), including isolated reports].

The table below summarizes the frequencies of local and systemic reactions solicited during the first 7 days that were recorded following the administration of INTANZA 9µg or an intramuscular trivalent inactivated influenza vaccine:

Adverse events	Adults 18-59 Years Intradermal 9 µg (N=2384)	Adults 18-59 Years Comparator Intramuscular 15 µg (N=843)
General disorders and Administration Site Conditions		
<u>Local reactions</u>		
Injection site erythema	85.0%	19.0%
Injection site swelling	62.7%	14.9%
Injection site induration	61.5%	19.9%
Injection site pain	41.9%	44.0%
Injection site pruritus	42.7%	9.1%
Injection site ecchymosis	8.3%	6.5%
<u>Systemic reactions</u>		
Malaise	17.3%	18.4%
Shivering	8.7%	8.0%
Pyrexia (Body temperature* $\geq 38.0^{\circ}\text{C}$)	3.8%	3.5%
Nervous system disorders		
Headache	30.2%	30.1%
Musculoskeletal and connective tissue disorders		
Myalgia	22.6%	29.5%

* Rectal equivalent temperature

Unsolicted reactions reported following the administration of INTANZA 9µg listed below were reported with the following frequencies:

General disorders and administration site conditions:

Uncommon Asthenia

Blood and lymphatic system disorders

Uncommon Lymphadenopathy

Nervous system disorders

Uncommon: Paraesthesia

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia

Skin and subcutaneous tissue disorders

Uncommon: Pruritus, rash

Rare: Sweating increased

Adverse Reactions from Post-Marketing Surveillance

There is no data from post-marketing experience with INTANZA 9µg. However, based on the experience with trivalent inactivated influenza vaccines administered by intramuscular or deep subcutaneous injection, systemic reactions, not listed above, may be reported.

Blood and lymphatic system disorders

Transient thrombocytopenia,

Immune system disorders

Allergic reactions, in rare cases leading to shock, angioedema

Nervous system disorders

Neuralgia, febrile convulsions, neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome

Vascular disorders

Vasculitis associated in very rare cases with transient renal involvement

Skin and subcutaneous tissue disorders

Generalised skin reactions including, urticaria

DOSAGE AND ADMINISTRATION

Adults from 18 to 59 years of age: 0.1 mL

Immunisation should be carried out by intradermal route using the Micro-Injection System.

The recommended site of administration is the region of the deltoid.

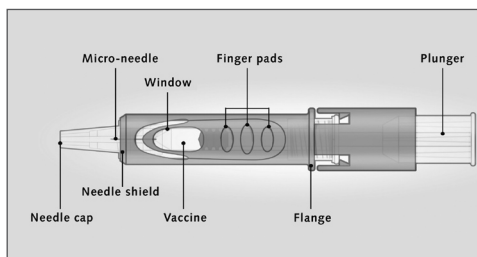
Any unused product or waste material should be disposed of in accordance with local requirements.

It is not necessary to shake the vaccine before use.

The Micro-Injection System for intradermal injection consists of a pre-filled syringe with a micro-needle (1.5mm) and a needle shielding system.

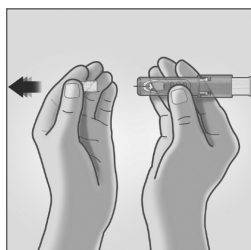
The needle shielding system is designed to cover the micro needle after use.

Micro-Injection System



Instructions for use:

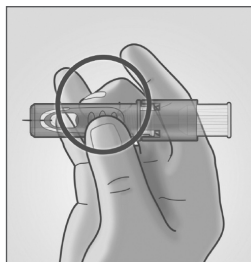
1 - REMOVE NEEDLE CAP



- Remove the needle cap from the micro-injection system.

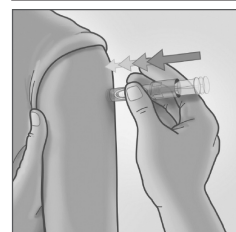
- Do not purge air through the needle

2 - HOLD MICRO-INJECTION SYSTEM BETWEEN THUMB & MIDDLE FINGER



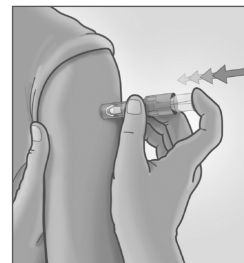
- Hold the intradermal system by placing the thumb and middle finger on the finger pads; the index finger remains free. Do not place the fingers on the windows.

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.

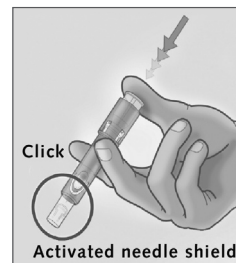
4 - INJECT USING THE INDEX FINGER



- 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.

- The vein test is unnecessary.

5 - ACTIVATE NEEDLE SHIELD BY PUSHING FIRMLY ON PLUNGER



- Remove the needle from the skin. Orient 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 intradermal system in the nearest sharps collector.

Injection is considered successful whether or not the presence of a wheal is observed.

In case of presence of liquid at the injection site after vaccine administration, revaccination is not required.

OVERDOSAGE

Overdosage is unlikely to have any untoward effect.

PRESENTATION AND STORAGE CONDITIONS

0.1 mL of suspension in a pre-filled syringe (type I glass) with a Micro-Injection System, with attached micro-needle, equipped with an elastomer plunger stopper (chlorobutyl), a tip cap (thermoplastic elastomer and polypropylene) and a needle shielding system. Pack size of 1 or 10.

Store in a refrigerator (2°C-8°C). Do not freeze. Keep the syringe in the outer carton in order to protect from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Only Medicine

DATE OF APPROVAL

16 March 2009

DATE OF MOST RECENT AMENDMENT

17 November 2009