PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PANENZA®

Pandemic Influenza vaccine (H1N1)v (split virion, inactivated)

Suspension for Intramuscular Injection

Active Immunizing Agent for the Prevention of Influenza

ATC code: J07BB02

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Toronto, Ontario, Canada
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RECENT MAJOR LABEL CHANGES

Not Applicable

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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

PANENZA® is indicated for prophylaxis of influenza in an officially declared pandemic situation in individuals 6 months of age and older.

The indication is based on immunological data from the vaccine containing the 2009 H1N1 pandemic strain (see section 14 CLINICAL TRIALS).

PANENZA should be used in accordance with official guidance.

1.1 Pediatrics

Pediatrics (> 6 months): The safety and immunogenicity of PANENZA has been established in pediatric patients 6 months of age and older (see section 7.1.3 Pediatrics). No data are available in children less than 6 months of age.

1.2 Geriatrics

Geriatrics (> 60 years of age): The safety and immunogenicity of PANENZA has been established in geriatric patients 60 years of age and older (see section 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

PANENZA should not be administered to anyone with a history of severe allergic reaction to egg or chicken proteins, or to any component of the vaccine or after previous administration of the vaccine or a vaccine containing the same components or constituents. For a complete listing, see 6

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Elderly, adults, and children from 3 years of age:
One dose (0.5 mL) of the vaccine given at an elected date. A second dose should be given after an interval of at least 3 weeks (see 7 WARNINGS AND PRECAUTIONS, Immune, Pediatrics and Geriatrics).

Children from 6 months to 35 months of age:
One half-dose (0.25 mL) of the vaccine is given at an elected date, followed by a second half-dose after an interval of at least 3 weeks.

Children less than 6 months of age:
PANENZA is not recommended in children less than 6 months of age.

4.4 Administration

Administration should be carried out by intramuscular injection (IM) preferably in the deltoid region.

The preferred site of administration is into the deltoid muscle, in adults and children >1 year of age. The preferred site for infants and young children (<1 year of age) is the anterolateral aspect of the thigh.

Do not inject by intravascular route (See 7 WARNINGS AND PRECAUTIONS, Hematologic).

The vaccine should be placed at room temperature for a few minutes and gently swirled between hands before use to obtain homogeneous suspension.

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

For each dose withdrawal and each patient, a new sterile syringe fitted with a new sterile needle should be used.

A partially used multidose vial must be discarded immediately if:

- Sterile dose withdrawal has not been fully observed.
- There is any suspicion that the partially used vial has been contaminated.
- There is visible evidence of contamination, such as change in appearance.

After use, any remaining vaccine and container must be disposed of safely according to local procedures.

4.5 Missed Dose

Not applicable for this vaccine.

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, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular	**Dosage Form:** Suspension for injection **Active Ingredients:** Each 0.5 mL dose contains 15 mcg hemagglutinin of the following strain: A/California/7/2009 (H1N1) pdm09-like strain	Disodium phosphate dihydrate, potassium chloride, potassium dihydrogen phosphate, sodium chloride, thiomersal and water for injections. **Manufacturing residuals**: formaldehyde, octoxynol-9, neomycin and egg proteins.

Description:

PANENZA is a non-adjuvanted vaccine supplied as a sterile, colorless limpid to opalescent suspension in a multidose vial (10 doses of 0.5 mL).

Active Ingredients:

Each 0.5 mL dose is formulated to contain 15 mcg hemagglutinin of influenza virus of the A/California/7/2009 (H1N1) pdm09-like strain propagated in eggs.

Note: The virus strain will be updated based on the pandemic virus strain recommended by the World Health Organization (WHO) at the time of the declaration of a pandemic.

Other Ingredients:

Thiomersal (45 mcg) and up to 0.5 mL Phosphate Buffered Saline solution (for 1000 mL: 1.15 g disodium phosphate dihydrate; 0.20 g potassium chloride; 0.20 g potassium dihydrogen phosphate; 8.00 g sodium chloride and water for injection (up to 1000 mL).

Manufacturing residuals: formaldehyde and octoxynol-9 are present in the final product. Each dose may contain trace amounts of neomycin, and egg proteins (including ovalbumin).

Packaging

The container closure system consists of a Type I glass vial closed with a chlorobutyl stopper and a flip-off cap.

The container closure system for PANENZA does not contain latex and is considered safe for use in persons with latex allergies.

7 WARNINGS AND PRECAUTIONS

General

In patients who have a history of serious or severe reaction following a previous injection with the same vaccine or a vaccine containing similar components, the risks and benefits of vaccination must be carefully considered (see 2 CONTRAINDICATIONS).

Caution is needed when administrating this vaccine to persons with a known hypersensitivity to the active substance, to any of the excipients or to residues listed in section 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

PANENZA should not be administered to persons with a history of severe allergic reaction to egg proteins (see 2 CONTRAINDICATIONS).

Formaldehyde and octoxynol-9 have been used in the manufacturing process of this product and are present in the final product, therefore an allergic reaction may occur.

Neomycin has been used in the manufacturing process of this product. As each dose may contain trace amounts of neomycin, caution must be exercised when the vaccine is administered to subjects with hypersensitivity to this antibiotic (and other antibiotics of the same class).

This vaccine contains thiomersal (an organomercuric compound) as a preservative and it is possible that an allergic reaction occurs.

The person responsible for administration must take all precautions known for the prevention of allergic or any other reactions.

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following administration of the vaccine. Epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be available to treat unexpected reactions (e.g., anaphylaxis).

Syncope can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

As with any vaccine, vaccination with PANENZA may not protect 100% of vaccinated individuals.

PANENZA, as now constituted, is not effective against all possible strains of influenza virus. Protection is limited to the strain of virus from which the vaccine is prepared or to closely related strains.

There are no safety, immunogenicity or efficacy data to support interchangeability of PANENZA with other influenza vaccines.

PANENZA should not be administered by intravascular injection.

Driving and Operating Machinery

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

Febrile

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

Hematologic

PANENZA should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Immune

In immunocompromised persons whether due to genetic defect, immunodeficiency disease, or immunosuppressive therapy, the immunological response to the vaccine could be reduced. Nevertheless, vaccination of immunocompromised persons is recommended even if the antibody response might be limited.

Neurologic

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give PANENZA should be based on careful consideration of the potential benefits and risks.

Monitoring and Laboratory Tests

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 results. The transient false positive reactions could be due to the IgM response by the vaccine.

7.1 Special Populations

7.1.1 Pregnant Women

Healthcare providers should assess the benefit and potential risks of administering the vaccine to pregnant women taking into consideration official recommendations.

Pregnant women are at high risk of influenza complications, including premature labour and delivery, hospitalisation, and death.

Data from prospective and observational studies during the 2009 H1N1 pandemic did not suggest any adverse maternal and fetal outcomes attributable to PANENZA. No concerns were raised regarding the safety of PANENZA following the administration of one or two doses, either in vaccinated subjects or newborns of women who were exposed during their pregnancy.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (> 6 months): Lower immune responses were observed in subjects aged 3 to 8 years

compared to subjects aged 9 to 17 years, and thus a second dose should be considered (see section 14 CLINICAL TRIALS).

7.1.4 Geriatrics

Geriatrics (> 60 years of age): Lower immune responses were observed in the elderly compared to adults aged 18 to 60 years, and thus a second dose should be considered (see section 14 CLINICAL TRIALS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of PANENZA has been assessed in three Phase II clinical trials conducted in France (Studies GPF07, GPF08) and Finland (GPF09) and from worldwide post-marketing experience during the 2009 H1N1 pandemic.

In the three Phase II clinical trials, local and systemic reactions were solicited within 7 days following two doses administration at a 21 days interval (see Tables 2, 3 and 4). Unsolicited adverse reactions were reported within 21 days after each injection, and with a six and twelve-month safety follow-up of serious adverse events (see section 8.3 Less Common Clinical Trial Adverse Reactions). No related serious adverse events and adverse events of special interest were reported during the trials.

Solicited reactions were mostly of Grade 1 (mild) to Grade 2 (moderate) in severity and usually resolved spontaneously within 1 to 3 days after onset. A few solicited reactions of Grade 3 (severe) in severity were reported in children (i.e. injection site erythema, fever, headache, malaise, myalgia) and usually resolved spontaneously or with medication within 8 days after onset. In subjects aged 6 to 24 months, rare and non-serious Grade 3 solicited reactions included injection site induration, appetited lost, crying abnormal, drowsiness, malaise and irritability.

In adults and elderly (over 60 years), the most frequent solicited reactions were headache, myalgia and injection site pain. Globally, reactions were more frequent in adults than in elderly. In adolescents from 9 to 17 years of age, the most frequent reactions were injection site pain and headache, malaise, myalgia and shivering. In children from 3 to 8 years of age, the most frequent reactions were injection site pain, injection site erythema, headache and malaise. Globally, reactions were more frequent in children and adolescents than in adults and elderly.

In children from 24 to 35 months of age, the most frequent reactions were injection site pain, injection site erythema and malaise. In infants from 6 to 23 months of age, the most frequent local reactions were injection site pain, injection site erythema and injection site induration. Different systemic reactions were solicited among infants and the most frequent were fever, crying abnormal, drowsiness, appetite lost and irritability.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adult and elderly

In an open-label clinical trial, two doses (0.5 mL) of PANENZA have been administered at a 3-week interval in 101 adults and 45 elderly. The data below summarizes the frequencies of the adverse reactions that were recorded following each vaccination (Table 2).

Table 2 - Frequency of local and systemic reactions solicited during the first 7 days following each administration of PANENZA (Study GPF07)

	Adults 18 – 60 years (N=101)		**Elderly** > 60 years (N=45)	
Local Reactions	**Post dose 1**	**Post dose 2**	**Post dose 1**	**Post dose 2**
Injection site pain	12.9%	18.8%	4.4%	15.9%
Injection site erythema	1.0%	1.0%	2.2%	0.0%
Injection site swelling	2.0%	2.0%	0.0%	0.0%
Injection site induration	0.0%	1.0%	0.0%	0.0%
Injection site ecchymosis	0.0%	0.0%	0.0%	2.3%
Systemic reactions	**Post dose 1**	**Post dose 2**	**Post dose 1**	**Post dose 2**
Malaise	7.9%	5.9%	8.9%	0.0%
Shivering	4.0%	4.0%	0.0%	0.0%
Headache	25.7%	12.9%	8.9%	11.4%
Myalgia	16.8%	16.8%	11.1%	11.4%
Fever (≥ 38°C)	1.0%	1.0%	0.0%	0.0%

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Children and adolescent (from 3 to 17 years of age)
In an open-label clinical trial, two doses (0.5 mL) of PANENZA have been administered at a 3-week interval in 51 children from 3 to 8 years of age and 52 adolescents from 9 to 17 years of age. The data below summarizes the frequencies of the adverse reactions that were recorded following each vaccination.

Table 3 - Frequency of local and systemic reactions solicited during the first 7 days following each administration of PANENZA (Study GPF08)

	Children 3 - 8 years (N=51)		**Adolescents** 9 - 17 years (N=52)	
Local Reactions	**Post dose 1**	**Post dose 2**	**Post dose 1**	**Post dose 2**
Injection site pain	45.1%	46.9%	61.5%	53.8%
Injection site erythema	13.7%	16.3%	9.6%	5.8%
Injection site swelling	5.9%	4.1%	3.8%	3.8%
Injection site induration	11.8%	4.1%	1.9%	3.8%
Injection site ecchymosis	9.8%	6.1%	1.9%	1.9%
Systemic reactions	**Post dose 1**	**Post dose 2**	**Post dose 1**	**Post dose 2**
Malaise	21.6%	14.3%	28.8%	13.5%
Shivering	9.8%	8.2%	15.4%	7.7%
Headache	21.6%	12.2%	40.4%	28.8%
Myalgia	11.8%	8.2%	25.0%	19.2%
Fever (≥ 38°C)	2.0%	4.1%	1.9%	3.8%

Children from 6 to 35 months of age

In an open-label clinical trial, two half-doses (0.25 mL) of PANENZA have been administered at a 3-week interval in 51 infants from 6 to 11 months of age and in 50 toddlers from 12 to 35 months of age either in the thigh or the deltoid muscle respectively. The data below summarizes the frequencies of the adverse reactions that were recorded following both the first and second dose. Solicited systemic reactions were defined differently between toddlers aged 12-23 months and 24-35 months of age, therefore these subgroups are listed separately.

Table 4 - Frequency of local and systemic reactions solicited during the first 7 days following any vaccination of PANENZA in children from 6 to 35 months (Study GPF09)

	Infants 6 – 11 months (N=51)		**Toddlers** 12 – 35 months (N=50)	
Local Reactions	**Post dose 1**	**Post dose 2**	**Post dose 1**	**Post dose 2**
Injection site pain / tenderness	9.8%	14.0%	30.6%	27.1%
Injection site erythema	13.7%	10.0%	14.3%	14.6%
Injection site swelling	3.9%	0.0%	10.2%	4.2%
Injection site induration	7.8%	12.0%	8.2%	6.3%
Injection site ecchymosis	3.9%	6.0%	12.2%	8.3%

	Infants 6 – 11 months (N=51)		**Toddlers** 12 – 23 months (N= 10**)**		**Toddlers** 24- 35 months (N=40)	
Systemic Reactions	**Post dose 1**	**Post dose 2**	**Post dose 1**	**Post dose 2**	**Post dose 1**	**Post dose 2**
Malaise	-	-	-	-	15.4%	15.8%
Shivering	-	-	-	-	2.6%	2.6%
Headache	-	-	-	-	2.6%	5.3%
Myalgia	-	-	-	-	10.3%	7.9%
Fever (≥ 38°C)	7.8%	10.0	10.0%	10.0%	2.6%	2.6%
Irritability	62.7%	50.0%	60.0%	20.0%	-	-
Drowsiness	25.5%	14.0%	40.0%	0.0%	-	-
Vomiting	5.9%	8.0	0.0%	0.0%	-	-
Abnormal crying	41.2%	34.0	40.0%	10.0%	-	-
Appetite lost	25.5%	34.0	40.0%	10.0%	-	-

8.3 Less Common Clinical Trial Adverse Reactions

Unsolicited adverse reactions within 21 days following any vaccination in adults

General disorders and administration site conditions: axillary pain, fatigue

Musculoskeletal and connective tissue disorders: myalgia

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Unsolicited adverse reactions within 21 days following any vaccination in pediatrics

Blood and lymphatic system disorders: leukopenia, leukocytosis, neutropenia, neutrophilia

Gastrointestinal disorders: abdominal pain upper, diarrhea, vomiting

General Disorders and Administration Site Conditions: axillary pain, diarrhea, fatigue, injection site injury, injection site hemorrhage, injection site pruritus, injection site rash, injection site warmth, irritability, swelling

Immune system disorders: allergic reaction, cutaneous allergic reaction

Infections and Infestations: nasopharyngitis, respiratory tract infection, rhinitis, tonsillitis

Metabolism and Nutrition Disorders: anorexia

Musculoskeletal and Connective Tissue Disorders: neck pain, torticollis

Nervous System Disorders: febrile seizures, paraesthesia

Psychiatric Disorders: insomnia

Respiratory , Thoracic and Mediastinal Disorders: bronchial asthma, cough, oropharyngeal pain, rhinorrhea

Skin and Subcutaneous Tissue Disorders: erythema, rash

8.5 Post-Market Adverse Reactions

In addition to the adverse reactions reported in clinical trials, the following adverse reactions have been reported very rarely during post-marketing surveillance with PANENZA, including with similar trivalent seasonal influenza vaccine formulations, even if an exact incidence rate cannot be precisely calculated:

Blood and lymphatic system disorders: transient lymphadenopathy, transient thrombocytopenia

Immune system disorders: allergic reactions, including anaphylactic reactions that may lead to shock, angioedema, dyspnea, pruritus, urticaria or non-specific rash

Nervous system disorders: arthralgia, asthenia, cataplexy, convulsions, encephalitis, encephalomyelitis, febrile seizures, Guillain-Barré syndrome, hypotonia, hypotonic-hyporesponsive episode, neuralgia, neuritis, paraesthesia

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

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

There are no data on co-administration of PANENZA with other vaccines. The vaccine should not be given at the same time as other vaccines.

If the vaccine is used in persons deficient in producing antibodies due to immunosuppressive therapy, the expected immune response may be limited (see 7 WARNINGS AND PRECAUTIONS, Immune).

Although an inhibition of hepatic clearance of phenytoin, theophylline and warfarin has been reported after influenza vaccination, subsequent studies have not shown any evidence of undesirable effects related to this phenomenon.

9.7 Drug-Laboratory Test Interactions

Following influenza vaccination, false-positive results in serology tests using the ELISA method to detect antibodies against HIV-1, hepatitis C and especially HTLV-1 have been observed. The Western blot technique may disprove the false-positive results and confirm the true results. The transient false positive reactions could be due to the IgM response by the vaccine.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The inoculation of antigen prepared from inactivated influenza virus stimulates the production of specific antibodies. Protection is afforded only against those strains of virus from which the vaccine is prepared or closely related strains.

10.2 Pharmacodynamics

Refer to 14 CLINICAL TRIALS for immunogenicity.

10.3 Pharmacokinetics

Duration of Effect

Information on duration of effect will be updated upon availability of data on the new pandemic strains (see 14 CLINICAL TRIALS).

11 STORAGE, STABILITY AND DISPOSAL

Keep out of the reach and sight of children.

Do not use PANENZA after the expiry date which is stated on the carton and the label.

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

After first opening, use PANENZA within 7 days if stored in a refrigerator (2°C to 8°C).

12 SPECIAL HANDLING INSTRUCTIONS

After first opening, the vaccine contained in the vial must be used within 7 days.

Partially used vials must be kept at the required temperature, i.e., between 2°C and 8°C (never place the product in a freezer).

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: Influenza vaccine (H1N1)v (split virion, inactivated)

Product Characteristics:

PANENZA is a sterile suspension of inactivated split influenza virus for intramuscular injection. PANENZA contains one strain of influenza virus cultivated on embryonated eggs, and then concentrated and purified by zonal centrifugation in a sucrose gradient. The split virion is obtained by octoxynol-9 treatment and inactivated by formaldehyde. The split viral strain is then blended by diluting in Phosphate Buffered Saline solution to the appropriate concentration. Thiomersal is added as preservative.

For the 2009 pandemic campaign, the reference viral strain A/California/7/2009 (H1N1) – derived NYMC X-179A is a reassortant strain between the A/California/7/2009 strain and A/New York/55/2004 (NYMC X-157) (H3N2) strain, generated by the New York Medical College (NYMC) and supplied by the Centers for Disease Control and Prevention.

In case of a pandemic, the strain to be included in the vaccine (variation) will be provided by a WHO Center, Essential Regulatory Laboratories or Candidate Vaccine reassortant Laboratories.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Prophylaxis Of Influenza

Three Phase II trials, multicenter, randomized, and open label with PANENZA were conducted during the 2009 H1N1 pandemic in healthy adults aged 18 to 60 years and elderly subjects aged > 60 years (Study GPF07), in children and adolescents from 3 to 17 years of age (Study GPF08), and in infants and toddlers from 6 to 35 months of age (Study GPF09). A summary of the studies is provided in Table 5.

Table 5- Summary of patient demographics for clinical trials in individuals 6 months of age and older

Study #	Study Design	Dosage and Route of Administration	Study Subjects	Mean Age (Range)	Male/Female %
GPF07	Phase II, multicenter, randomized, open trial in healthy adults and elderly	0.5 mL Intramuscular injection	*Adults*: N= 101 *Elderly*: N=45	*Adults:* 44.3 years (18 to 60) *Elderly:* 71.0 years (60 to 85)	*Adults and Elderly:* 47/54
GPF08	Phase II multicenter randomized open trial in healthy children and adolescents	0.5 mL Intramuscular injection	*Children:* N= 52 *Adolescents:* N=52	*Children:* 6 years (3 to 9) *Adolescents:* 12.5 years (9 to 17)	*Children:* 40/60 *Adolescents:* 59/41
GPF09	Phase II multicenter randomized open-label trial in healthy infants and toddlers	0.25 mL *(infants)* or 0.5 mL Intramuscular injection	*Infants:* N= 51 *Toddlers:* N=50	*Infants:* 9 months (6-11) *Toddlers:* 27 months (13 to 35)	*Infants:* 47/53 *Toddlers:* 58/42

N= number of subjects

Participants 3 years of age and older received two full dose (0.5 mL) of the non-adjuvanted H1N1 vaccine containing 15 µg of hemagglutinin (HA) administered 21 days apart. Infants and toddlers aged 6 to 35 months received two half-dose (0.25 mL) administered 21 days apart.

Immunogenicity was assessed 21 days after each injection of PANENZA. Anti-HA antibody titers were measured by the Hemagglutination Inhibiting (HI) method and neutralizing antibody titers by the Seroneutralisation (SN) method.

For anti-HA antibodies (HI method), immunogenicity endpoints included:
- percentage of subjects who achieved seroprotection with post-vaccination titers ≥40 (1/dilution);
- percentage of subjects who achieved seroconversion, defined as post-vaccination titers ≥ 40 in subjects with a pre-vaccination titer < 10, or ≥ four-fold increase in titers from pre- to post-vaccination for subjects with a pre-vaccination titer ≥ 10;

- individual geometric mean titer ratio (post-/pre-vaccination titers).

For neutralizing antibodies (SN method), the immunogenicity endpoint was the percentage of subjects with ≥ four-fold increase in titers from pre- to post-vaccination.

Additionally, anti-HA antibody persistence was assessed at 8 months after the first dose of PANENZA, as defined as the percentage of subjects with titers ≥ 40.

14.3 Immunogenicity

Study GPF07

Adults and elderly: Following the first vaccination with PANENZA, almost all subjects had a detectable antibody titer in both age groups, and at least 93.0% of adult subjects and 83.7% of elderly subjects were seroprotected against the A/H1N1 influenza strain (Table 6). A second dose of PANENZA did not elicit further significant increase of immune responses in adults, but resulted in higher immune responses in elderly. After the second vaccination, at least 98.0% of adult subjects and at least 95% of elderly subjects raised seroprotective antibody titers against the A/H1N1 influenza strain.

Table 6– Seroprotection Rate, Seroconversion Rate, and the Geometric Mean Ratio in Adults and Elderly (Study GPF07)

	Adults (18 to 60 years of age) N= 101		**Elderly** (over 60 years of age) N= 45	
	21 days after 1st dose	**21 days after 2nd dose**	**21 days after 1st dose**	**21 days after 2nd dose**
Hemagglutination inhibiting (HI) method				
Seroprotection rate % [95% CI]	93.0 % [86.1; 97.1]	98.0 % [93.0; 99.8]	83.7 % [69.3; 93.2]	95.3 % [84.2; 99.4]
Seroconversion rate % [95% CI]	92.0 % [84.8; 96.5]	96.0 % [90.2; 98.9]	81.4 % [66.6; 91.6]	90.7 % [77.9; 97.4]
Geometric mean ratio [95% CI]	48.7 [35.6; 66.5]	58.7 [45.0; 76.7]	18.5 [11.7; 29.3]	28.1 [18.5; 42.8]
Seroneutralisation (SN) method				
4-fold increase % [95% CI]	96.0 % [90.1; 98.9]	97.0 % [91.5; 99.4]	88.6 % [75.4; 96.2]	86.4 % [72.6; 94.8]

Point estimates are presented with their 95% confidence intervals (CI)

After 8 months in a subset of 50 adults and 44 elderly subjects, 84% of subjects who received two doses of vaccine remained seroprotected against the A/H1N1 strain with anti-HA titers ≥ 40.

Study GPF08

Children and adolescent (from 3 to 17 years of age): In children aged 3-8 years, 94.0% and 100% of subjects developed seroprotective antibody titers (≥ 40 [1/dil]) against the pandemic A/H1N1 influenza strain 21 days after the first and second vaccination with PANENZA, respectively.

In children aged 9-17 years, 98.1% and 100% of subjects developed seroprotective antibody titers against the pandemic A/H1N1 influenza strain 21 days after the first and second vaccination with PANENZA, respectively.

Table 7- Seroprotection Rate, Seroconversion Rate, and the Geometric Mean Ratio in Children and Adolescents from 3 to 17 Years of Age (Study GPF08)

	Children (3 to 8 years of age) N= 52		**Adolescents** (9 to 17 years of age) N= 52	
	21 days after 1st dose	**21 days after 2nd dose**	**21 days after 1st dose**	**21 days after 2nd dose**
Haemagglutination inhibiting (HI) method				
Seroprotection rate % [95% CI]	94.0 % [83.5; 98.7]	100 % [92.9; 100]	98.1 % [89.7; 100]	100 % [93.2; 100]
Seroconversion rate % [95% CI]	94.0 % [83.5; 98.7]	100 % [92.9; 100]	98.1 % [89.7; 100]	100 % [93.2; 100]
Geometric mean ratio [95% CI]	35 [24.0; 51.1]	163 [119; 223]	125 [81.9; 190]	238 [179; 316]
Seroneutralisation (SN) method				
4-fold increase % [95% CI]	96.0 % [86.3; 99.5]	100 % [92.9; 100]	100 % [93.2; 100]	100 % [93.2; 100]

After 8 months in a subset 29 children and 33 adolescents, at least 93% of subjects who received two doses of vaccine had seroprotective antibody titers.

Study GPF09

Children from 6 to 35 months of age: In infants aged 6-11 months, 32.7% and 98.0% of subjects developed seroprotective antibody titers (≥ 40 [1/dil]) against the pandemic A/H1N1 influenza strain 21 days after the first and second vaccination with half dose PANENZA, respectively.

In toddlers aged 12-35 months, 34.0% and 97.9% of subjects developed seroprotective antibody titers against the pandemic A/H1N1 influenza strain 21 days after the first and second vaccination with half dose PANENZA, respectively.

Table 8- Seroprotection Rate, Seroconversion Rate, and the Geometric Mean Ratio in Children from 6 to 35 Months of Age (GPF09)

	Infants (6 to 11 months of age) N= 51		**Toddlers** (12 to 35 months of age) N= 50	
	21 days after 1st dose	**21 days after 2nd dose**	**21 days after 1st dose**	**21 days after 2nd dose**
Hemagglutination inhibiting (HI) method				
Seroprotection rate % [95% CI]	32.7 [19.9; 47.5]	98.0 [89.1; 99.9]	34.0 [20.9; 49.3]	97.9 [88.7; 99.9]
Seroconversion rate % [95% CI]	32.7 [19.9; 47.5]	98.0 [89.1; 99.9]	34.0 [20.9; 49.3]	97.9 [88.7; 99.9]
Geometric mean titer ratio [95% CI]	3.67 [2.82; 4.79]	36.9 [28.5; 47.7]	5.66 [3.96; 8.08]	48.7 [34.7;68.3]
Seroneutralisation (SN) method				
4-fold increase % [95% CI]	77.6 [63.4; 88.2]	100.0 [92.7;100.0]	85.1 [71.7; 93.8]	97.9 [88.7; 99.9]

After 8 months in a subset 12 infants and 23 toddlers, 66.7% of subjects aged 6 to 11 months and 95.7% of subjects aged 12 to 35 months who received two half-doses of vaccine remained seroprotected to the A/H1N1 strain.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Data in animals from inactivated non-adjuvanted seasonal influenza vaccines (containing thiomersal as preservative at 45 mcg/dose) revealed no special hazard for humans based on conventional local tolerance repeated dose toxicity and developmental and reproductive toxicity studies.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PANENZA

Pandemic Influenza vaccine (H1N1)v (split virion, inactivated), suspension for injection

Read this carefully before you start taking PANENZA 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 PANENZA.

What is PANENZA used for?

PANENZA is a non-adjuvanted vaccine used to prevent influenza (flu) caused by a pandemic virus in individuals 6 months of age and older.

Pandemic influenza is caused by a new influenza virus in which people have no prior immunity and can spread rapidly around the world. The signs of a pandemic flu are similar to those of a regular flu but may be more serious.

How does PANENZA work?

When a person is given the vaccine, the immune system (the body's natural defense system) will produce its own protection (antibodies) against the disease. None of the ingredients in the vaccine can cause the flu.

The vaccine is given by injection with a needle in the upper arm and may require two doses given three weeks apart. Children and the elderly may not be optimally protected until after receiving the second dose of the vaccine.

As with all vaccines, PANENZA may not fully protect all persons who are vaccinated.

What are the ingredients in PANENZA?

Medicinal ingredients: Each 0.5 mL dose of PANENZA contains 15 micrograms of hemagglutinin of the Influenza virus (inactivated, split virion) of the following strain:

A/California/7/2009 (H1N1)

Non-medicinal ingredients: disodium phosphate dihydrate, potassium chloride, potassium dihydrogen phosphate, sodium chloride, thiomersal (45 micrograms per 0.5 mL dose), and water for injections.

Other ingredients: trace amounts of egg and chicken proteins, neomycin, octoxynol-9, and formaldehyde.

PANENZA comes in the following dosage forms:

Suspension for injection in a multidose vial

Do not use PANENZA if:

- if you previously had a sudden life-threatening allergic reaction to any ingredient of PANENZA or to any of the substances that may be present in trace amounts, or following a previous influenza vaccine
- if you have a severe infection with a high temperature. Your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor should advise whether you could still be vaccinated with PANENZA.

If you are not sure, talk to your doctor or pharmacist before having this vaccine.

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

- had an allergic reaction to any ingredient contained in the vaccine, to thiomersal, to egg or chicken proteins, or other influenza vaccination.
- have a bleeding problem such as a coagulation disorder.
- have a low immunity due to a disease or treatment that suppress the immune system.
- have had Guillain-Barré syndrome within 6 weeks of receiving a previous vaccine.
- are pregnant or breastfeeding.

Other warnings you should know about:

In the first few weeks after vaccination with PANENZA, the results of blood tests to look for certain virus infection may not be correct. Tell the doctor requesting these tests that you have recently been given PANENZA.

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

PANENZA should not be given at the same time as other vaccines.

How to take PANENZA:

For adults and children >1 year of age, inject the vaccine into the deltoid muscle.

For infants and children <1 year of age, inject the vaccine in the anterolateral aspect of the thigh.

Usual dose:

Individuals 3 years of age and older: Two doses of 0.5 mL administered with an interval of at least 21 days between doses.

Children from 6 months to 35 months of age: Two half-doses of 0.25 mL administered with an interval of at least 21 days between doses.

PANENZA is not recommended in children less than 6 months of age.

Overdose:

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

Missed Dose:

Not applicable for this vaccine.

What are possible side effects from using PANENZA?

These are not all the possible side effects you may have when taking PANENZA. If you experience any side effects not listed here, tell your healthcare professional.

Allergic reactions may occur following vaccination, in rare cases leading to shock. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. Healthcare professionals are aware of this possibility and have emergency treatment available for use in such cases.

The following side effects of PANENZA are very common (more than 1 in 10 people) or common (between 1 to 10 in 100 people):
- Injection site: pain, redness, swelling, hardening, and bruising
- Headache
- Muscular pain
- Feeling unwell
- Shivering
- Fever

In children 6 to 23 months of age, the following additional side effects of PANENZA are very common or common:
- Drowsiness
- Abnormal crying
- Lost of appetite
- Irritability
- Vomiting

Most of these side effects usually disappeared without treatment within 1 to 3 days after onset. In children aged less than 3 years, some side effects may disappear within 8 days after onset, or require medication such as for the treatment of fever or pain.

Very rarely, vasculitis (inflammation of blood vessels) temporarily affecting the kidneys, and neurological disorders (affecting the nerves and brain) such as paresthesia, neuritis and Guillain Barré syndrome have been reported.

The serious side effects listed below have occurred after vaccination with PANENZA or with similar vaccines to prevent the flu.

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional**	
	Only if severe	**In all cases**
VERY RARE (1 in 10 000 people)		✓
Allergic Reactions: rash, itching or hives on the skin, swelling of the face, lips, tongue, or other parts of the body		✓
Anaphylaxis: difficulty breathing, dizziness, a weak and rapid pulse, skin rash, vomiting, fainting		✓
Febrile seizure: fever, brief convulsion or fit of uncontrolled body movements		✓
Guillain-Barré Syndrome: muscle weakness and pain, feeling of pins and needles, paralysis		✓
Lymphadenopathy: temporary swelling of the glands in the neck, armpit or groin		✓
Neuritis: pain, weakness, numb and tingly arms		✓
Thrombocytopenia: temporary reduction in blood platelets can result in bruising or bleeding, red skin spots		✓
Vasculitis: purple colored skin spots, swollen blood vessel, pain, and in very rare cases kidney problems		✓

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 Limited 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 in a refrigerator at 2° to 8°C. Do NOT freeze. Keep the vial in the outer carton in order to protect from light.

After first opening, use PANENZA within 7 days if stored in a refrigerator (2° to 8°C).

Do not use after the expiration date.

Keep out of reach and sight of children.

If you want more information about PANENZA:

- 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 Sanofi Canada website (www.sanofi.ca), or by calling 1- 888-621-1146.

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