

PRODUCT MONOGRAPH

^DINFLUVAC[®]
influenza vaccine, surface antigen, inactivated

Suspension for Injection

Each 0.5 mL pre-filled syringe contains neuraminidase and 15 mcg haemagglutinin of each virus strain as recommended by the WHO and NACI.

Active Immunizing Agent for the Prevention of Influenza
ATC Code: J07BB02

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^DINFLUVAC[®]

influenza vaccine, surface antigen, inactivated

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection or deep subcutaneous injection	0.5 mL pre-filled syringe containing neuraminidase and 15 mcg haemagglutinin per virus strain in a suspension	INFLUVAC may contain traces of eggs (such as ovalbumin, chicken proteins), formaldehyde, cetyltrimethylammonium bromide, polysorbate 80, or gentamicin, which are used during the manufacturing process. <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING SECTION.</i>

DESCRIPTION

INFLUVAC (influenza vaccine, surface antigen, inactivated) is a trivalent subunit influenza vaccine. Each 0.5 mL dose contains neuraminidase and 15 mcg of haemagglutinin antigen for each virus strain present in the vaccine. The composition of INFLUVAC is adapted annually to comply with the World Health Organization (WHO) and the National Advisory Committee on Immunization (NACI) recommendations (northern hemisphere). The virus strains used in the vaccine for 2018/2019 are:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage).

INFLUVAC is a colourless clear liquid. INFLUVAC is thimerosal-free, mercury-free, and contains no preservative.

INDICATIONS AND CLINICAL USE

INFLUVAC (influenza vaccine, surface antigen, inactivated) is indicated for the prevention of influenza infection caused by the specific strains contained in the vaccine, in adults and children from 3 years of age.

Refer to the Canadian Immunization Guide for the most recent recommendations:
<https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html>

CONTRAINDICATIONS

The influenza virus for INFLUVAC (influenza vaccine, surface antigen, inactivated) is propagated in chicken eggs; therefore, this vaccine should not be administered to anyone with a history of hypersensitivity (allergy) and especially anaphylactic reactions to eggs or egg products.

Allergic reactions are extremely rare and are usually attributable to extreme sensitivity to certain components of the vaccine, probably to trace amounts of residual egg protein.

INFLUVAC should not be given to people who have a hypersensitivity to the active substances, to any of the excipients or to any component that may be present as traces such as eggs, chicken protein (such as ovalbumin), formaldehyde, cetyltrimethylammonium bromide, polysorbate 80, or gentamicin. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

Allergic or anaphylactic reactions to a previous dose of influenza vaccine are contraindications for vaccination.

Immunization with INFLUVAC should be deferred in the presence of any acute illness, including acute or unstable neurologic illness, febrile illness, or active infection.

A minor febrile illness such as mild upper respiratory infection is not usually reason to defer immunization.

WARNINGS AND PRECAUTIONS

General

If INFLUVAC (influenza vaccine, surface antigen, inactivated) is used in persons receiving immunosuppressive therapy, including corticosteroid therapy, the expected immunological response may be diminished. Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

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

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

INFLUVAC should not be administered into the buttocks due to varying amounts of fatty tissue in this region, nor by the intradermal route, since these methods of administration may induce a weaker response.

INFLUVAC must not be administered intravascularly.

Sterile epinephrine HCl solution (1:1000) and other appropriate agents should be made available for immediate use in case of an anaphylactic reaction or if acute hypersensitivity to the vaccine occurs. Health care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.

Before administration of any vaccine, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccine, determination of previous immunization history, and the presence of any contraindications to immunization, current health status, and a current knowledge of the literature concerning the use of the vaccine under consideration.

Intramuscular injections should be given with care in persons suffering from coagulation disorders or on anticoagulant therapy because of risk of hemorrhage.

Pneumococcal vaccine and influenza vaccine can be given at the same visit but at different sites with separate sterile needles and syringes without an increase in side effects. Whereas influenza vaccine is given annually, pneumococcal vaccine should generally be given only once to adults.

Influenza virus undergoes significant antigenic changes from time to time, so different vaccines are made every year. INFLUVAC, 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.

The use of fractional doses in an attempt to reduce the severity of adverse reactions cannot be recommended because there is insufficient evidence on the safety or efficacy of such smaller doses.

As with any vaccine, immunization with INFLUVAC may not protect 100% of susceptible individuals.

Hematologic

See **ADVERSE REACTIONS**

Neurologic

See **ADVERSE REACTIONS**

Sensitivity/Resistance

See **ADVERSE REACTIONS**.

Special Populations

Pregnant Women:

Inactivated influenza vaccines, such as INFLUVAC, can be used in all stages of pregnancy. Larger datasets on safety are available for the second and third trimester, compared with the first trimester; however, data from worldwide use of influenza vaccine do not indicate any adverse foetal and maternal outcomes attributable to the vaccine.

Nursing Women:

Evidence indicates that influenza vaccine is safe for breastfeeding mothers.

Fertility:

No fertility data are available

Pediatrics:

INFLUVAC is indicated in children 3 years of age and older. The safety and efficacy of INFLUVAC in children less than 3 years of age have not been established. (See **CLINICAL TRIALS** and **REFERENCES** sections).

Geriatrics (> 65 years of age):

INFLUVAC is indicated in people 65 years of age and over (see **INDICATIONS AND CLINICAL USE**).

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 to the vaccine.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Vaccination with INFLUVAC (influenza vaccine, surface antigen, inactivated) cannot cause influenza because the vaccine does not contain live virus.

Local reactions include: redness, swelling, itching, warmth, pain, restriction in arm movement, induration and ecchymosis. The most frequent local reaction is soreness at the injection site lasting up to 2 days in adults but rarely interferes with normal activities. Prophylactic acetaminophen may decrease the frequency of pain at the injection site.

Systemic reactions: fever, increased sweating, headache, malaise, shivering, myalgia, arthralgia, and fatigue. The most frequent systemic reaction is headache.

Allergic responses to influenza vaccine, which in rare cases could lead to anaphylactic shock, are probably a consequence of hypersensitivity to some vaccine component.

Neurological disorders which have been reported in persons after influenza vaccination include neuritis, encephalomyelitis, febrile convulsions and paresthesia.

Rare cases of systemic vasculitis have been reported in persons after influenza vaccination, but a causal relation has not been established.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

A total of 1856 patients have been given INFLUVAC with thimerosal or INFLUVAC thimerosal-free in clinical trials. The safety of INFLUVAC was assessed in the following clinical trials: annual strain composition update requirement, including at least 50 adults aged 18-60 years and at least 50 elderly subjects aged 60 years or older, conducted during the period of 1993 to 2002 using INFLUVAC with thimerosal; a study comparing INFLUVAC thimerosal-free and INFLUVAC with thimerosal; a study with INFLUVAC thimerosal-free; and a study of 52 high-risk children (6 months to 4 years) vaccinated with INFLUVAC with thimerosal.

Safety evaluation (i.e. local and systemic reactogenicity) is performed during the first 3 days following vaccination.

The following undesirable effects have been observed during clinical trials with the following frequencies (Table 1).

Table 1. Summary of adverse events observed during clinical trials

System Organ Class	Common $\geq 1/100$, $< 1/10$
Nervous system disorders	Headache*
Skin and subcutaneous tissue disorders	Sweating*
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia*
General disorders and administration site conditions	Fever, malaise, shivering, fatigue Local reactions: redness, swelling, pain, ecchymosis, induration*.

*These reactions usually disappear within 1-2 days without treatment.

Data on reactogenicity can be found in Table 2.

Table 2. Local and systemic reactions during three days after vaccination with INFLUVAC without thimerosal (n=197)

Total N=197	Adults N=144 (aged 18 – 59 years) % (n)	Elderly N=53 (aged 60 years and over) % (n)
Local reactions		
Redness	17.4 (25)	3.8 (2)
Swelling	11.8 (17)	3.8 (2)
Itching	3.5 (5)	7.5 (4)
Warmth	7.6 (11)	5.7 (3)
Pain on contact	41.7 (60)	5.7 (3)
Continuous pain	3.5 (5)	1.9 (1)
Restriction in arm movement	13.2 (19)	3.8 (2)
Induration	16.7 (24)	1.9 (1)
Ecchymosis	4.2 (6)	3.8 (2)
Systemic reactions		
Increased sweating	3.5 (5)	3.8 (2)
Headache	11.8 (17)	1.9 (1)
Malaise	2.8 (4)	3.8 (2)
Insomnia	3.5 (5)	3.8 (2)
Shivering	2.1 (3)	0.0 (0)

Data from clinical studies with INFLUVAC thimerosal-free show local reactions occurred most frequently the first day after vaccination (37.1%) and declined during the second and third day to 30.5 % and 14.7% respectively. As for the systemic reactions, few participants to the study reported systemic reactions, and the numbers reported remained stable during the first three days (8.6%, 7.6% and 5.1% respectively).

As summarized in Table 3, both local and systemic reactions for both formulations are comparable. The most frequent local reaction was pain on contact (31% and 32% for the thimerosal- containing and thimerosal-free vaccine, respectively), and the most frequent systemic reaction was headache (11% and 9% for the thimerosal-containing and thimerosal-free vaccine, respectively).

Table 3. Comparison of reactogenicity on thimerosal-free vs. thimerosal-containing INFLUVAC

Measure	Thimerosal-free INFLUVAC n=197 % (n)	thimerosal-containing INFLUVAC n=1692 % (n)
Pain on contact at vaccination site	32% (63)	31% (52)
Headache	9% (18)	11% (19)
Any local symptom	45% (89)	45% (76)
Any systemic symptom	14% (28)	19% (32)
Moderate or severe inconvenience	0% (0)	3% (51)

Safety in high-risk children

A clinical study in high-risk children with chronic respiratory or congenital heart disease aged 6 months to 4 years with thimerosal-containing INFLUVAC (Table 4), showed that the vaccine was well tolerated. Following either of the two vaccinations, the incidence of any local (23%) and any systemic reactions (48%) in this particular group was considered comparable with those

reported in healthy adults. These children received two separate vaccinations and had the added parameters of loss of appetite, increased crying and irritability. All reactions were recorded in the questionnaire by the parent/guardian (instead of direct reporting). The reactions recorded were relatively minor in nature and were resolved within a few days.

Table 4. Reported vaccine reactions after vaccination (72 hrs) with thimerosal-containing INFLUVAC in high-risk children aged 6 months to 4 years

	Distribution of Reactions after:											
	1 st vaccination				2 nd vaccination				Any vaccination			
	Yes		No		Yes		No		Yes		No	
	N	%	N	%	N	%	N	%	N	%	N	%
Any Local Reactions	8	15	44	85	7	14	44	86	12	23	40	77
Any Systemic Reactions	17	33	35	67	12	24	39	76	25	48	27	52
Any Reactions	23	44	29	56	14	27	37	73	29	56	23	44

Although a total of fifteen serious adverse events were reported in thirteen of the children (as defined by hospitalization) these were relatively minor events. Due to the underlying chronic respiratory or congenital heart disease in these patients and their young age, it is understandable for their physician to hospitalize them, even in case of minor events which could otherwise be treated at home. Four of the serious adverse events were arranged admissions (for cardiac catheterization (3) or jejunal biopsy).

Only two of these serious adverse events (in two subjects) were thought by the investigators to be possibly related to the vaccine: “Increased cough and diarrhea”, and “Pyrexia, runny nose and cough”.

Safety in asthmatic children

Safety data of INFLUVAC with thimerosal was presented in a recent publication on an investigator initiated placebo controlled study in 6-18 year old asthmatic children, who had taken asthma medication in the year previous to the study. The study was performed during two consecutive influenza seasons (1999-2000 and 2000-2001), but individual patients could only participate for one season. A total of 696 children participated in this study of which 347 were vaccinated with thimerosal-containing INFLUVAC. Influenza-related asthma exacerbations were of comparable number and severity in the group vaccinated with the vaccine and the placebo group. It was found that the duration of the exacerbations was 3 days shorter in the group vaccinated with the INFLUVAC. No serious adverse events to the vaccine were observed in this study.

Post-Market Adverse Drug Reactions

Adverse reactions reported from post marketing surveillance are, in addition to the reactions which have also been observed during clinical trials, the following:

Blood and lymphatic system disorders:

Transient thrombocytopenia, transient lymphadenopathy

Immune system disorders:

Allergic reactions, in rare cases leading to shock, angioedema

Nervous system disorders:

Neuralgia, paraesthesia, 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:

Generalized skin reactions including pruritus, urticaria or non-specific rash

Guillain-Barré Syndrome (GBS) occurred in adults in association with the 1976 swine influenza vaccine, and evidence favours the existence of a causal relation between the vaccine and GBS during that season. In an extensive review of studies since 1976, the United States Institute of Medicine concluded that the evidence is inadequate to accept or reject a causal relation between GBS in adults and influenza vaccines administered after the swine influenza vaccine program in 1976.

In Canada the background incidence of GBS was estimated at just over 20 cases per million population in a study done in Ontario and Quebec. A variety of infectious agents, such as *Campylobacter jejuni*, have been associated with GBS. It is not known whether influenza virus infection itself is associated with GBS. Neither is it known whether influenza vaccination is causally associated with increased risk of recurrent GBS in persons with a previous history of GBS. Avoiding subsequent influenza vaccination of persons known to have developed GBS within 6 to 8 weeks of a previous influenza vaccination appears prudent at this time. The reporting rate of GBS associated with INFLUVAC is concluded to remain within the expected back-ground incidence.

Influenza vaccine is not known to predispose to Reye's Syndrome.

Oculorespiratory Syndrome (ORS) has been reported sporadically in Canada, US and Europe following influenza immunization. Starting in the 2000/2001 season, ORS is defined as the onset of bilateral red eyes and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness or sore throat) and/or facial swelling occurring within 24 hours of influenza immunization. The pathophysiologic mechanism underlying ORS remains unknown.

After the 2000-2001 influenza season, fewer ORS cases have been reported to Health Canada. Please refer to the *Canadian Immunization Guide* for further details about administration of vaccine and management of adverse events.

Physicians, nurses and pharmacists should report any immediate adverse reactions arising from any vaccination, or following shortly thereafter, in accordance with local requirements and to the

manufacturer: Drug Safety, BGP Pharma ULC, 85 Advance Rd., Etobicoke, ON M8Z 2S6
Canada. Telephone: 1-844-596-9526.

DRUG INTERACTIONS

Overview

No interaction between INFLUVAC (influenza vaccine, surface antigen, inactivated) and other vaccines or medication are known.

Drug-Drug Interactions

INFLUVAC may be given at the same time as other vaccines. Immunization 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.

Theophylline and Anticoagulants

Influenza vaccine can inhibit the clearance of theophylline and anticoagulants such as warfarin. However, clinical studies have not shown any adverse effects attributable to these drugs in people receiving influenza vaccine.

Drug-Food Interactions

Not known.

Drug-Herb Interactions

Not known.

Drug-Laboratory Interactions

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.

Drug-Lifestyle Interactions

Effects on ability to drive and use machines

INFLUVAC has no or negligible influence on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose of INFLUVAC for adults and children from 3 years of age is 0.5 mL. For children, who have not previously been vaccinated, a second dose should be given after an interval of at least 4 weeks.

Administration

Parenteral biological products should be inspected visually for extraneous particulate matter and/or discoloration before administration. If these conditions exist, the product should not be administered.

For information on vaccine administration, see the current Canadian Immunization Guide and the Health Canada Website.

The patient should be given 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. Thus the permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.

INFLUVAC should be administered by intramuscular or deep subcutaneous injection.

INFLUVAC is a colourless clear liquid, in pre-filled single-dose syringes with / without a needle.

INFLUVAC should be allowed to reach room temperature (15-25°C) before use.

For syringes without a needle, remove the cap and attach a needle.

Shake the pre-filled syringe well to uniformly distribute the suspension before administration.

Remove the needle protection, and bleed the syringe of air while holding the needle pointing vertically upward by pressing the plunger in slowly.

Do not administer intravascularly.

Needles should not be recapped, and the syringe should be disposed of properly.

Reconstitution: INFLUVAC comes as 0.5 mL suspension ready for injection.

OVERDOSAGE

Overdosage is unlikely to have any untoward effect.

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

ACTION AND CLINICAL PHARMACOLOGY

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

INFLUVAC (influenza vaccine, surface antigen, inactivated) is an egg-grown, inactivated influenza virus subunit, trivalent vaccine based on isolated surface antigens of A and B strains of

myxovirus influenza. 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.

Influenza A viruses are classified into subtypes on the basis of 2 surface antigens: haemagglutinin (H) and neuraminidase (N). Three subtypes of haemagglutinin (H1, H2, H3) and 2 subtypes of neuraminidase (N1, N2) are recognized among influenza A viruses that have caused widespread human disease. Immunity to these antigens, especially to the haemagglutinin, reduces the likelihood of infection and lessens the severity of disease if infection occurs. Infection with a virus of one subtype confers little or no protection against viruses of other subtypes. Antigenic variation over time within a subtype may be so marked that infection or vaccination with one strain may not induce immunity to distantly related strains of the same subtype. Although influenza B viruses have shown more antigenic stability than influenza A viruses, antigenic variation does occur. For these reasons, major epidemics of respiratory disease caused by variants of influenza still occur. The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the virus strains included in each year's vaccine.

Each year's influenza vaccine contains 3 virus strains representing the influenza viruses that are likely to be circulating in Canada on the basis of the recommendation from the World Health Organization for the northern hemisphere.

Pharmacodynamics

Protective antibody levels are generally obtained within 2 to 3 weeks after vaccination.

Pharmacokinetics

As this is a vaccine product, pharmacokinetic studies are not applicable.

Duration of Effect

Protective antibody titres generally last for at least 6 months and may last up to one year or longer. New influenza vaccines are produced each year according to the WHO recommended composition. Patients vaccinated a short time before the start of the expected influenza activity (November in the Northern Hemisphere) may therefore be expected to be protected for influenza infections or its complications during the whole influenza season (November to April).

Serological data over a 52-week period since vaccination in healthy adult subjects aged 18 to 60 years showed a substantial decrease in antibody titres, as is to be expected for Influenza vaccines. Still the 52-week GMT values are markedly elevated as compared to the pre-vaccination values. The observed decline in GMT values over a one year period was approximately 50-70% for both strains. The sustained levels of protective antibody titres are in line with the expectation of protection during an influenza season up to 6 months after vaccination.

STORAGE AND STABILITY

INFLUVAC (influenza vaccine, surface antigen, inactivated) should be stored at 2 to 8°C (in a refrigerator). Do not freeze. Store in the original package in order to protect from light.

Do not use vaccine after expiration date as stated on the label.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

SPECIAL HANDLING INSTRUCTIONS

INFLUVAC (influenza vaccine, surface antigen, inactivated) should be allowed to reach room temperature (15-25°C) before use. Ensure that the product is returned to the refrigerator within 24 hours if not used.

Shake well before use. Inspect visually prior to administration.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

INFLUVAC (influenza vaccine, surface antigen, inactivated) is supplied as a suspension for injection in pre-filled syringes (glass, type I) with/ without a needle.

Composition

Each single dose (0.5 mL) contains:

Active Ingredients

For the 2018/2019 season, each dose of INFLUVAC contains neuraminidase and 15mcg of haemagglutinin of the following virus strains:

- A/Michigan/45/2015 (H1N1)pdm09-like strain (A/Singapore/GP1908/2015, IVR-180);
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain (A/Singapore/INFIMH-16-0019/2016, NIB-104);
- B/Colorado/06/2017-like strain (B/Victoria/2/87 lineage) (B/Maryland/15/2016, NYMC BX-69A).

Other Ingredients

Excipients

Potassium chloride	0.1 mg
Potassium dihydrogen phosphate	0.1 mg
Disodium phosphate dihydrate	0.67 mg
Sodium chloride	4.0 mg
Calcium chloride dihydrate	0.067 mg
Magnesium chloride hexahydrate	0.05 mg
Water for Injection	To 0.5 mL

Manufacturing Process Residuals

INFLUVAC may also contain trace amounts of eggs, chicken protein, formaldehyde, cetyltrimethylammonium bromide, polysorbate 80 and gentamicin.

INFLUVAC is thimerosal-free, mercury-free, and contains no preservative.

Packaging

INFLUVAC is supplied in prefilled glass syringes with/ without a needle, containing 0.5 mL suspension for injection. The syringes are made of neutral glass Type 1. The container closure system for INFLUVAC is free of latex.

INFLUVAC is available in the following formats:

Single pack- syringe is packed in a tamper evident carton box.

Ten pack- syringes are packed in a tamper evident carton box for 10 syringes.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

- Proper name: Influenza virus subunit vaccine (surface antigen, inactivated).
- Chemical name: Monovalent Bulk containing inactivated haemagglutinin and neuraminidase surface antigens of WHO/NACI recommended strains of influenza virus.
- Physiochemical properties: The Monovalent Bulk is a clear to slightly opalescent liquid. The pH of the Monovalent Bulk is in the range 6.9 to 7.5.

Product Characteristics

This vaccine complies with the WHO and NACI recommendations (northern hemisphere) for the 2018-2019 season. The active substances are:

Influenza virus surface antigens (haemagglutinin and neuraminidase) of the following strains:

- A/Michigan/45/2015 (H1N1)pdm09-like strain (A/Singapore/GP1908/2015, IVR-180);
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain (A/Singapore/INFIMH-16-0019/2016, NIB-104);
- B/Colorado/06/2017-like strain (B/Victoria/2/87 lineage) (B/Maryland/15/2016, NYMC BX-69A).

The virus strain is supplied as a primary seed virus by the NIBSC (National Institute for Biological Standards and Control, Potters Bar, UK), or by another designated WHO laboratory. The primary seed virus is propagated in embryonated SPF (specific pathogen-free) hens' eggs to generate a master seed virus (MSV). The working seed virus (WSV) is generated by the propagation of the MSV in embryonated SPF hens' eggs.

The WSV is diluted to a seed suspension and then inoculated in embryonated eggs. The inoculated eggs are incubated for approximately 3 days. After incubation, the eggs are cooled to $5 \pm 3^{\circ}\text{C}$ for 12 - 48 hours.

The allantoic fluid is harvested from the eggs and clarified using a centrifuge to remove cell and egg debris. The clarified allantoic fluid of the single harvest of a strain is separated in a zonal gradient centrifuge (0-60% sucrose). The virus containing fractions with approximately 47 to 35% m/m of sucrose are collected and inactivated by formaldehyde treatment in two stages, first for 18 hours to 3 days and secondly for 4 to 10 days. The inactivated fractions are pooled, filtered and diluted with PBS. The sucrose and formaldehyde is removed by ultrafiltration. The haemagglutinin and neuraminidase are solubilised by the addition of Polysorbate 80 and CTAB.

The non-solubilised remainders of the virus particles are removed by centrifugation. The CTAB and the Polysorbate 80 are removed from the supernatant by adsorption to an adequate quantity of Amberlite XAD-4 resin. After adsorption of the detergents, the Amberlite resin is removed by filtration. PBS is added and the final suspension is sterilised by filtration which is the Monovalent Bulk vaccine.

The manufacture of the drug product (=final lot) involves blending three monovalent bulks, and diluting the drug substance with buffers to produce the final (=trivalent) bulk. The final bulk is filled into single-dose syringes, using an Isolator filling machine to produce the final product.

CLINICAL TRIALS

Study demographics and trial design

Data analysis includes 24 vaccination studies conducted with INFLUVAC (influenza vaccine, surface antigen, inactivated) with thimerosal during the period between 1993-2002, study comparing INFLUVAC (influenza vaccine, surface antigen, inactivated) thimerosal-free and INFLUVAC with thimerosal, and an annual update study with INFLUVAC thimerosal-free. An overview of exposure and demographic data is given in Tables 5-6. A total of 1659 subjects of 6 months and older were vaccinated with standard doses of INFLUVAC with thimerosal: 1010 healthy adults (18 – 60 years), 597 healthy elderly (>60 years), 85 healthy adults aged 18 – 60 years in a comparative trial and 52 high-risk children (6 months to 4 years) (Table 6). A total of 197 subjects of 18 years and older were vaccinated with standard doses of INFLUVAC thimerosal-free (Table 5): 84 subjects aged 18 – 60 years in a comparative trial, 60 healthy subjects aged 18 – 60 years in an annual strain update study and 53 healthy elderly aged 60 years and over in an annual strain update study.

Table 5. Demographic Data on INFLUVAC thimerosal-free

Study number	Trial Design	Dosage, route of administration and duration	Number of vaccinees	Mean age (range)	Gender N _{male} /N _{female}
25 ¹	Double blind, randomized, parallel groups	0.5 mL pre-filled syringe containing neuraminidase and 15 mcg haemagglutinin per viral strain, intramuscular or deep subcutaneous injection, and 3 weeks	84	38.3 (18-59)	44/40
26 ² (adults)	Open, Baseline controlled	0.5 mL pre-filled syringe containing neuraminidase and 15 mcg haemagglutinin per viral strain, intramuscular or deep subcutaneous injection, and 3 weeks	60	29.8 (18-59)	16/44
26 ² (elderly)	Open, Baseline controlled	0.5 mL pre-filled syringe containing neuraminidase and 15 mcg haemagglutinin per viral strain, intramuscular or deep subcutaneous injection, and 3 weeks	53	68.2 (60-79)	26/27

¹ Comparative, double blind parallel study with thimerosal-free INFLUVAC and the standard INFLUVAC. Here, only the data for the thimerosal-free INFLUVAC were included.

² Previously separate annual update studies were performed for (young) adults (≥ 18 and ≤ 60 years of age) and elderly subjects (>60 years); in recent annual update studies both age groups participate in the same protocol.

³ In 2003 no separate annual update study was necessary since the composition of the strains had not changed since the previous Influenza season.

Table 6. Demographic Data on INFLUVAC thimerosal-containing INFLUVAC in High-Risk children aged 6 months to 4 years

Study number	Trial Design	Dosage, route of administration and duration	Number of vaccinees	Mean age (range)	Gender N _{male} /N _{female}
27	Open, Baseline controlled	0.25 mL pre-filled syringe containing neuraminidase and 15 mcg haemagglutinin per viral strain, intramuscular or deep subcutaneous injection, and 4 weeks	52 ¹	19.5 months (6-48months)	25/27

¹ 52 children that started with the study, of which 51 actually completed the entire study period.

Study results

Immunogenicity

Immunogenicity data consisted of pre- and post-vaccination titres per subject and vaccine strain, determined in duplicate. After logarithmic transformation, immunogenicity parameters as requested by the CHMP (Table 7) were calculated per study: mean fold increase (MFI), numbers of subjects exceeding a protective titre of 40 after vaccination (seroprotection (SP_{post})), and numbers of at least fourfold titre rise (seroconversion (SC)). Moreover, pre- and post-vaccination geometric mean titre (GMT), and numbers of subjects exceeding a protective titre of 40 prior to vaccination (SP_{pre}), were determined.

Table 7. Criteria for assessment of influenza vaccines, according to the CHMP

Age class	Serological parameter	Criteria
Adults 18 to 60 years of age	MFI	> 2.5
	SP (% of subjects exceeding a titre of 40)	> 70%
	SC (% of subjects with seroconversion or at least 4-fold titre rise)	> 40%
Adults ≥60 years of age (Elderly)	MFI	> 2.0
	SP (% of subjects exceeding a titre of 40)	> 60%
	SC (% of subjects with seroconversion or at least 4-fold titre rise)	> 30%

In all 26 studies in young and elderly adults the current CHMP requirement for sufficient immunogenicity (meeting at least one of the criteria for each of the three strains) was met. In fact, in 24 of the 26 studies all three criteria were met for all strains in the vaccine. The absence of thimerosal did not affect the immunogenicity of the vaccine, as all three CHMP criteria for all three strains were met and no differences were found compared to the thimerosal-containing product.

Since there are no CHMP-criteria for children, the CHMP criteria for adult subjects were used to evaluate the data from high-risk children. The CHMP-requirement for immunogenicity was met in this specific population of young children at risk.

Tables 8 and 9 show the serological parameters for all studies in adults/elderly, according to (sub)type. The serological response as measured by a number of parameters was excellent in most cases, which confirms previous observations.

For INFLUVAC with thimerosal all of the 74 MFI-values and SC-values exceeded the CHMP - criteria, as well as 71 of 74 SP_{post}-values. In 44 cases, SP_{post}-values were even greater than 90%. In three studies, SP_{post}-values of some strains did not reach the value as required by the CHMP: Study nr. 2 (elderly) for virus strains A-H₁N₁ and B and Study nr. 9 (young adults) for virus strain A-H₃N₂. The overall CHMP requirement was still met in these three studies (i.e. the other CHMP criteria for these strains were compliant). For the INFLUVAC thimerosal-free, the CHMP criteria for MFI, SC and SP_{post} were met in all three strains used.

The comparative study analysed the effect of the absence of the preservative thimerosal on the immunogenicity of the vaccine. The results obtained in the study (Tables 8 and 9) show that the absence of the preservative does not have any effect on the efficacy of the vaccine.

In the study with high-risk children aged 6 months to 4 years (Table 10), the vaccine induced a strong immunogenic response against all three haemagglutinin antigens. In fact, the CHMP - requirement applicable to adults/elderly was also met for this specific group.

Table 8. Serological parameters for the INFLUVAC thimerosal-free - Pre- and post-GMT, MFI, Pre- and post-SP, and SC

Study ^{nr.}	Subtype	N	GMT _{pre} [*]	GMT _{post} [*]	MFI [*]	SP _{pre} [*]	SP _{post} [*]	SC [*]	
25 ¹	A-H ₃ N ₂	84	13.4 (10.4 – 17.3)	254.8 (207.0 – 313.7)	19.0 (14.1 – 25.7)	23 (14 – 32)	98 (94 – 100)	85 (77 – 92)	
	A-H ₁ N ₁	84	5.8 (5.1 – 6.6)	131.2 (99.7 – 172.5)	22.7 (17.2 – 29.9)	4 (0 – 8)	86 (78 – 93)	82 (74 – 90)	
	B	84	5.1 (4.9 – 5.4)	71.2 (53.9 – 94.0)	13.9 (10.6 – 18.3)	0	77 (68 – 86)	77 (68 – 86)	
26 ²	A-H ₃ N ₂	59 [†]	30.9 (21.3 – 44.8)	385.5 (337.4 – 440.4)	12.5 (8.3 – 18.8)	58 (44 – 70)	100 (94 – 100)	75 (62 – 85)	
	adults	A-H ₁ N ₁	59 [†]	7.5 (5.8 – 9.6)	307.5 (263.1 – 359.5)	41.0 (30.7 – 54.9)	12 (5 – 23)	100 (94 – 100)	93 (84 – 98)
	B	59 [†]	14.5 (10.6 – 19.8)	250.5 (217.3 – 288.9)	17.3 (13.2 – 22.7)	34 (22 – 47)	100 (94 – 100)	97 (88 – 100)	
26 ² elderly	A-H ₃ N ₂	53	34.5 (22.6 – 52.6)	262.2 (205.4 – 334.8)	7.6 (5.0 – 11.5)	53 (39 – 67)	96 (87 – 100)	64 (50 – 77)	
	A-H ₁ N ₁	53	13.5 (9.8 – 18.5)	106.8 (84.7 – 134.7)	7.9 (5.3 – 11.9)	32 (20 – 46)	96 (87 – 100)	62 (48 – 75)	
	B	53	20.9 (14.8 – 29.6)	182.9 (152.8 – 219.0)	8.7 (6.1 – 12.5)	42 (28 – 56)	98 (90 – 100)	75 (62 – 86)	

* Geometric means and 95% confidence intervals;

¹ Subjects vaccinated with INFLUVAC thimerosal-free in study S201.3.118

² The annual update 2004 (protocol S201.3.120) studied adults and elderly populations in one protocol. From 60 subjects 18-60 years of age, one subject's data were excluded for serology sampling because of an intercurrent infection during the study.

† Proportion (x 100%) and 95% confidence intervals

GMT = Geometric Mean Titre; MFI = Mean Fold Increase; SP = Seroprotection; SC = Seroconversion

Table 9. Serological parameters for the INFLUVAC thimerosal-free and INFLUVAC thimerosal containing- Pre- and post-GMT, MFI, Pre- and post-SP, and SC

Study ^{nr.}	Subtype	N	GMT _{pre} [*]	GMT _{post} [*]	MFI [*]	SP _{pre} [*]	SP _{post} [*]	SC [*]
25 ¹	A-H ₃ N ₂	84	13.4 (10.4 – 17.3)	254.8 (207.0 – 313.7)	19.0 (14.1 – 25.7)	23 (14 – 32)	98 (94 – 100)	85 (77 – 92)
	A-H ₁ N ₁	84	5.8 (5.1 – 6.6)	131.2 (99.7 – 172.5)	22.7 (17.2 – 29.9)	4 (0 – 8)	86 (78 – 93)	82 (74 – 90)
	B	84	5.1 (4.9 – 5.4)	71.2 (53.9 – 94.0)	13.9 (10.6 – 18.3)	0	77 (68 – 86)	77 (68 – 86)
25 ^{**}	A-H ₃ N ₂	83	18.6 (14.1 – 24.5)	231.5 (185.8 – 288.4)	12.4 (8.8 – 17.6)	35 (25 – 45)	98 (94 – 100)	70 (60 – 80)
	A-H ₁ N ₁	83	5.9 (5.2 – 6.6)	107.9 (82.1 – 142.0)	18.3 (13.9 – 24.2)	4 (0 – 8)	84 (77 – 92)	82 (74 – 90)
	B	83	5.9 (5.3 – 6.6)	61.3 (45.1 – 83.5)	10.3 (7.6 – 14.2)	2 (0 – 6)	72 (63 – 82)	67 (57 – 78)

¹ Subjects vaccinated with INFLUVAC thimerosal-free in study S201.3.118

^{**} Subjects vaccinated with thimerosal-containing INFLUVAC in study S201.3.118

GMT = Geometric Mean Titre; MFI = Mean Fold Increase; SP = Seroprotection; SC = Seroconversion

Table 10. Serological parameters for the thimerosal-containing INFLUVAC - Pre- and post-GMT, MFI, Pre- and post-SP, and SC; high-risk children aged 6 months to 4 years

Study nr	Subtype	N	GMT _{pre} * [†]	GMT _{post} * [†]	MFI*	SP _{pre} †	SP _{post} †	SC†
27	A-H ₃ N ₂	51	13.1 (8.7 – 19.6)	76.2 (40.9 – 142.2)	5.8 (4.3 – 7.9)	25 (14 – 40)	55** (40 – 69)	55 (40 – 69)
	A-H ₁ N ₁	51	5.2 (4.8 – 5.6)	56.0 (38.1 – 82.3)	10.8 (7.5 – 15.4)	2 (0 – 11)	71 (56 – 83)	71 (56 – 81)
	B	51	6.2 (5.1 – 7.6)	65.3 (44.3 – 96.4)	10.5 (7.4 – 14.8)	6 (1 – 17)	71 (56 – 83)	69 (54 – 81)

* Geometric means and 95% confidence intervals;

† Proportion (x 100%) and 95% confidence intervals

** Compared to the CPMP criteria for adults and elderly subjects, postvaccination seroprotection levels were met for the A-H₁N₁ and B strains. The A-H₃N₂ strain showed a somewhat lower response though still offering protection to a large group of vaccinees.

GMT = Geometric Mean Titre; MFI = Mean Fold Increase; SP = Seroprotection; SC = Seroconversion

Pediatric Studies

The pediatric indication for INFLUVAC is supported by studies published between 1997 and 2014 in healthy and high risk children aged 3 to 17 years of age (See **REFERENCES**).

DETAILED PHARMACOLOGY

Specific pre-clinical studies have not been conducted for INFLUVAC.

MICROBIOLOGY

Specific pre-clinical studies have not been conducted for INFLUVAC.

TOXICOLOGY

Specific pre-clinical studies have not been conducted for INFLUVAC.

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PART III: CONSUMER INFORMATION

^DINFLUVAC[®]

influenza vaccine, surface antigen, inactivated

This leaflet is Part III of a three-part "Product Monograph" published when INFLUVAC was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INFLUVAC. Contact your doctor or pharmacist if you have any further questions about this vaccine.

ABOUT THIS MEDICATION

What the medication is used for:

INFLUVAC is a vaccine used to prevent people from developing influenza (the flu), or reduce flu symptoms.

What it does:

Like other influenza vaccines, INFLUVAC causes the body to produce antibodies against the virus. This means that when your body is exposed to the flu virus, your body is able to defend itself. The antibodies stop the attacking virus. You cannot catch influenza from INFLUVAC since it only contains portions of the virus, and not the whole live virus. Your body takes 10 to 21 days to produce antibodies after vaccination. Therefore, if you are exposed to influenza immediately before or after your vaccination, you could still develop the illness. The vaccine will not protect you against the common cold, even though some of the symptoms are similar to influenza. Influenza viruses change all the time, so different vaccines may be made every year. To stay protected against influenza, you need to be re-vaccinated every year before the winter season.

It is particularly important for some groups of people to be vaccinated. These include people with certain medical conditions, elderly people, people who are likely to be exposed to the infection and people on certain medications. If you are in doubt as to whether you should be vaccinated, talk to your local health care professionals.

INFLUVAC complies with the World Health Organization (WHO) and National Advisory Committee on Immunization (NACI) recommendations for vaccination in the northern hemisphere for the 2018/2019 season.

When it should not be used:

INFLUVAC vaccine is made in eggs; therefore this vaccine should not be given to anyone with allergies and especially severe allergies (anaphylactic reactions) to chicken eggs or egg products.

INFLUVAC should not be given to people who have allergies to the active substances, to any of the excipients and to residues of eggs, chicken protein, formaldehyde, cetyltrimethylammonium bromide, polysorbate 80, or gentamicin. For a complete listing of

excipients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Anyone who has experienced allergic reactions to a previous dose of influenza vaccine SHOULD NOT be vaccinated with INFLUVAC.

What the medicinal ingredient is:

The medicinal ingredient is surface antigens neuraminidase and haemagglutinin of the following viruses as recommended by WHO and the NACI: an A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage).

What the other ingredients are:

Potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, sodium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, and water for injection.

For a full listing of other (non-medicinal) ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

What dosage forms it comes in:

INFLUVAC comes in a 0.5 mL pre-filled syringe for injection, List no. 0W184, containing neuraminidase and 15 mcg haemagglutinin of each of the following virus strains:

- A/Michigan/45/2015 (H1N1)pdm09-like strain (A/Singapore/GP1908/2015, IVR-180);
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain (A/Singapore/INFIMH-16-0019/2016, NIB-104);
- B/Colorado/06/2017-like strain (B/Victoria/2/87 lineage) (B/Maryland/15/2016, NYMC BX-69A).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
INFLUVAC should not be used in individuals who are allergic to eggs, previous doses of the flu vaccine, or any components of the flu vaccine.

BEFORE you use INFLUVAC talk to your doctor or pharmacist if:

- you are allergic to eggs or egg-products
- you are allergic to any of the following: formaldehyde, cetyltrimethylammonium bromide, polysorbate 80 or gentamicin
- you have a fever, or you think you may be getting a fever
- you had a serious reaction to any flu vaccine in the past
- you have any known allergies
- you have experienced any health problems
- you are pregnant
- you are currently on any medication (i.e., immunosuppressants, theophylline, anticoagulants such as warfarin).

Fainting, feeling faint or other stress related reactions can occur following, or even before, any needle injection. Therefore tell your doctor or nurse if you have

experienced this kind of reaction with a previous injection.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with INFLUVAC include: immunosuppressants, theophylline, anticoagulants such as warfarin.

PROPER USE OF THIS MEDICATION

Usual Dose:

One dose of 0.5 mL pre-filled syringe containing neuraminidase and 15 mcg haemagglutinin per viral strain as recommended by WHO and NACI.

Adults and children from 3 years of age: 0.5 mL, single dose. For children, who have not previously been vaccinated, a second dose should be given after an interval of at least 4 weeks.

INFLUVAC comes as a 0.5 mL suspension, ready for intramuscular or deep subcutaneous injection. Allow the vaccine to reach room temperature (15-25°C) before use. Ensure that the product is returned to the refrigerator within 24 hours if not used.

Shake well before use.

Overdose:

Overdosage is unlikely to have any bad effect.

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

Occasionally people have side effects with influenza vaccines. The most common of these are fever, feeling unwell, shivering, tiredness, headache, sweating, muscle or joint pain, and warmth. Skin reactions include redness, swelling, pain, ecchymosis (blue/black staining of the skin), a hardening of the skin at the injection site and itching.

These reactions will normally disappear without treatment in a day or two.

Rarely, neuralgia (nerve pain), paresthesia (numbness and tingling), convulsions (seizures) and temporary thrombocytopenia (a blood disorder) have been reported. In rare cases, allergic reactions may lead to shock.

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

Allergic reactions (this might include but is not limited to breathing or swallowing difficulties, or swelling in the face or skin), and temporary enlargement of the lymph nodes have been reported.

If you think that you have a side effect not mentioned here, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	fever	X		
	feeling unwell	X		
	shivering	X		
	tiredness	X		
	headache	X		
	sweating	X		
	muscle or joint pain	X		
	<u>Skin Reactions</u>			
	redness	X		
	swelling	X		
	pain	X		
	ecchymosis (blue/black staining of the skin)	X		
	reddening of the skin at the injection site	X		
Uncommon	nerve pain		X	
	numbness and tingling		X	
	convulsions (seizures)		X	
	temporary thrombocytopenia (a blood disorder)		X	
	allergic reactions		X	
	inflammation of blood vessels		X	
	temporarily affecting the kidneys		X	
	brain disorders		X	
	Guillain Barré syndrome		X	

This is not a complete list of side effects. For any unexpected effects while taking INFLUVAC, contact your doctor or pharmacist.

HOW TO STORE IT

INFLUVAC should only be given by a health care professional

Store INFLUVAC at 2 to 8°C (in a refrigerator).

Do not freeze. Store in the original package in order to protect from light.

Do not use after the expiry date.

This vaccine is effective against this year's 2018/2019 influenza virus.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following vaccination.

For Health Care Professionals:

If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events Following Immunization (AEFI) Form and send it to your local Health Unit in **your province/territory**.

For the General Public:

Should you experience an adverse event following immunization, please ask your doctor, nurse or pharmacist to complete the Adverse Events Following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact the Vaccine Safety Section at the Public Health Agency of Canada.

By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
E-mail: caefi@phac-aspc.gc.ca
Web: <http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>

Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, A/L 6502A
Ottawa, ON K1A 0K9

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

The most recent version of this document plus the full Product Monograph, prepared for health care professionals, can be found at: www.hc-sc.gc.ca (Drug Product Database) or at www.mylan.ca or by contacting the sponsor, BGP Pharma ULC, Etobicoke, Ontario, M8Z 2S6 at: 1- 844-596-9526

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