INSTITUTO BUTANTAN

trivalent influenza vaccine (split virion, inactivated)

2022 SEASON - Southern Hemisphere

[Description]

The trivalent influenza vaccine (split virion, inactivated) for intramuscular or deep subcutaneous use, is a sterile suspension containing 3 strains of influenza virus propagated in embryonated hens' eggs, concentrated, purified by zonal centrifugation, split by Triton® X-100, inactivated by formaldehyde and then diluted in buffered saline solution. The type and amount of viral antigens contained in the trivalent influenza vaccine (split virion, inactivated) conform to the current requirements of the World Health Organization (WHO). The strains for the 2022 season of southern hemisphere are: A/Victoria/2570/2019, IVR- 215 (H1N1), A/Darwin/9/2021, NIB-126 (H3N2) and B/ Austria/1359417/2021, BVR-26.

[Composition]

Each 0.5 mL dose of trivalent influenza vaccine (split virion, inactivated) contains three strains* of *Myxovirus influenzae* virus for the 2022 season of southern hemisphere, equivalent to:

15 µg of hemagglutinin (HA).....A/Victoria/2570/2019, IVR-215 (H1N1)

15 µg of hemagglutinin (HA).....A/Darwin/9/2021, NIB-126 (H3N2)

15 µg of hemagglutinin (HA).....B/Austria/1359417/2021, BVR-26

thimerosal (preservative)….....2 micrograms
buffered saline solution .....up to 0.5 mL
*propagated in embryonated hens´ eggs from healthy chicken flocks.

Composition of buffered saline solution at pH = 7.2: sodium chloride, potassium chloride, di-sodium hydrogen phosphate dihydrate, potassium dihydrogen phosphate anhydrous and water for injection.
Each dose of 0.5 mL of the vaccine may contain up to 30 micrograms of formaldehyde, traces of neomycin, Triton-X-100 (octoxynol-9) and ovalbumin.

Each 0.25 mL dose of trivalent influenza vaccine (split virion, inactivated) contains three strains* of *Myxovirus influenzae* virus for the 2022 season of southern hemisphere, equivalent to:

7.5 µg of hemagglutinin (HA)..... A/Victoria/2570/2019, IVR-215 (H1N1)

7.5 µg of hemagglutinin (HA)..... A/Darwin/9/2021, NIB-126 (H3N2)

7.5 µg of hemagglutinin (HA).....B/Austria/1359417/2021, BVR-26

thimerosal (preservative)….....1 microgram
buffered saline solution .....up to 0.25 mL

*propagated in embryonated hens´ eggs from healthy chicken flocks.

Composition of buffered saline solution at pH = 7.2: sodium chloride, potassium chloride, di-sodium hydrogen phosphate dihydrate, potassium dihydrogen phosphate anhydrous and water for injection.

Each dose of 0.25 mL of the vaccine may contain up to 15 micrograms of formaldehyde, traces of neomycin, Triton-X-100 (octoxynol-9) and ovalbumin.

[Indications]

The trivalent influenza vaccine (split virion, inactivated) is indicated for active immunization against influenza caused by the specific strains of influenza virus contained in the vaccine in adults and children 6 months of age and older.

[Administration]

The trivalent influenza vaccine (split virion, inactivated) is supplied as a slightly whitish, opalescent suspension in a vial. The vaccine vial should be gently shaken before use to homogenize the suspension. The vaccine should not be used if there is color changes or if foreign particles are present. The administration of the vaccine should be made by intramuscular or deep subcutaneous route. Do not use the intravenous route.
For children from 6 to 35 months of age the preferred site for intramuscular injection is the anterolateral aspect of the thigh. The preferred site for intramuscular injection for adults and children from 36 months of age is into the muscle of the upper arm.

[Immunization Schedule]

Vaccination should be performed yearly, preferably in the period prior to the highest circulation of influenza virus, and the vaccine recommended by the World Health Organization for the period should be used.
For children aged 6 to 35 months the recommended dose is 0.25 mL. For children not previously vaccinated, it is recommended the administration of a second dose of 0.25 mL with 1-month interval.
For children aged 36 months to 8 years the recommended dose is 0.5 mL. For children not previously vaccinated, it is recommended the administration of a second dose of 0.50 mL with 1-month interval.
For adults and children over 9 years: 1 dose of 0.5 mL.

[Side Effects]

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of trivalent influenza vaccine (split virion, inactivated) causing serious harm is extremely small. The small risks associated with trivalent influenza vaccine (split virion, inactivated) are much less than the risks associated with getting the disease against which it protects. The trivalent influenza vaccine (split virion, inactivated) cannot cause influenza because it does not contain any live virus.

- Very common side effects observed from clinical studies (≥ 10%):
  - Systemic: headache, myalgia (in both groups), malaise (in adults aged 18 to 59 years), weakness.
  - Local: itchiness (in adults aged 18 to 59 years), redness, swelling, pain, hardening.
- Common side effects observed from clinical studies (≥ 1% and < 10%):
  - Systemic: sweating, joint pain, fever, malaise (in > 60 years), shivering (in both groups), weakness.
  - Local: itchiness (in > 60 years), bruising (in both groups). These reactions tend to disappear in about one or two days without the need for treatment.
- Side effects observed in post-marketing monitoring:
  - Skin reactions that may spread over the body including itchiness, hives and rash (exanthema).
  - Nerve route pain, numbness and needles sensation, febrile seizures, inflammation of the brain and spinal cord, nerve inflammation, and Guillain-Barré syndrome (muscle weakness of the legs and arms and sometimes paralysis).
  - Temporary reduction in the number of platelets and temporary swelling of the lymph nodes.
  - Blood vessels inflammation with transient renal involvement in very rare cases (<0.01%).

Allergic reactions:
- Leading to shock in rare cases (≥ 0.01% and < 0.1%);
- Angioedema in very rare cases (< 0.01%);
- The occurrence of anaphylactic reaction is very rare.

This vaccine contains thimerosal as preservative and hypersensitivity reactions may occur.

[Contraindications]

Do not use trivalent influenza vaccine (split virion, inactivated) in individuals with:

- ✓ History of severe allergic reaction to egg proteins (egg or egg products), chicken proteins, any component of the vaccine (that is, as defined in the composition, including manufacturing residues) or after previous administration of this vaccine or to other vaccine containing the same components.
- ✓ Moderate or severe acute febrile disease. Vaccination should be postponed until the symptoms have disappeared.
- ✓ **This vaccine is contraindicated for children younger than 6 months of age.**

[Warnings and Precautions for Use]

- ✓ The vaccine should not, under any circumstance, be administered by intravenous route.
- ✓ Although the vaccine contains only traces of neomycin, Triton-X-100 (octoxynol-9) and formaldehyde, any previous allergic reaction to these components, including antibiotics of the same class as neomycin, should be taken into account by the patient´s physician.
- ✓ The protection provided by the vaccine is related only to the strains of the influenza virus composing the vaccine or which are closely related.
- ✓ The immune response may not be reached if the vaccine is used in immunocompromised persons (whether from disease or treatment).
- ✓ Vaccination should be carefully evaluated in patients with ongoing neurological disorders.
- ✓ Guillain-Barré Syndrome (GBS) may occur up to six to twelve months after flu vaccination with an incidence of one to two cases out of one million people vaccinated. There is an increased risk of GBS in individuals over 45 years.
- ✓ The vaccine should be administered with caution in individuals with low platelets or clotting impairment, since bleedings may occur following an intramuscular administration to these patients.
- ✓ The vaccine may be given at the same time as other vaccines by using separate limbs and different syringes. In this case, side effects may be intensified.
- ✓ The vaccine may interfere with the interpretation of some laboratory tests (false-positive reactions have been observed in serology tests after vaccination).

[Use in Specific Populations]

Use during Pregnancy: Reproductive toxicity in animals or clinical trials with pregnant women was not performed with the trivalent influenza vaccine (split virion, inactivated). Data from worldwide use of the vaccine in countries where trivalent influenza vaccines (split virion, inactivated) are recommended in all pregnancy stages [Weekly Epidemiological Record (WER) 2012, 87, 461-476], do not indicate any fetal and maternal adverse effects attributable to the vaccine. Please refer to national recommendations for guidance on the use of trivalent influenza vaccine (split virion, inactivated) during pregnancy.

Nursing Mothers: There is no data in newborns/infants born to women vaccinated with trivalent influenza vaccine (split virion, inactivated) while breastfeeding. However, based on the experience with the use of this type of vaccine, it may be used during breastfeeding.

Pediatric use: The trivalent influenza vaccine (split virion, inactivated) may be used for immunization of children from 6 months. After immunization, the occurrence of

adverse events such as fever, fatigue, weakness and muscle pain is more common in infants and children.

Geriatric use: The trivalent influenza vaccine (split virion, inactivated) is not likely to cause problems or adverse events in the elderly, different from those occurring in young adults, and there are no specific situations limiting the use of the vaccine in elderly patients. After immunization, elderly patients may present lower antibody titers than those obtained in young adults and may therefore remain susceptible to upper respiratory tract infections caused by the influenza virus. However, even if the efficacy of the vaccine may be lower in this group when compared to healthy young adults, elderly patients are highly benefited from vaccination as the vaccine provides high protection against flu-associated complications, frequent in this age group and which are responsible for hospitalizations and death.

[Storage]

The trivalent influenza vaccine (split virion, inactivated) should be stored in a refrigerator at +2 °C to +8 °C (35 ° to 46 °F). Do not freeze. Protect from light. Discard product if it has been exposed to freezing. Do not use the vaccine after the expiration date. Keep in its original package.
Once opened, the vaccine should be used within 7 days, as long as kept under aseptic conditions and at a temperature of +2 ºC to +8 ºC (35 ° to 46 °F). As long as maintained under refrigeration, the expiration date for the trivalent influenza vaccine (split virion, inactivated) is 12 months, from the manufacturing date. The expiration date refers to the last day of the month.

Keep the vaccine out of children's reach.
Before use verify whether the vaccine vial monitor (VVM), if attached, has not reached the discard point (see figure below).

[Presentation]

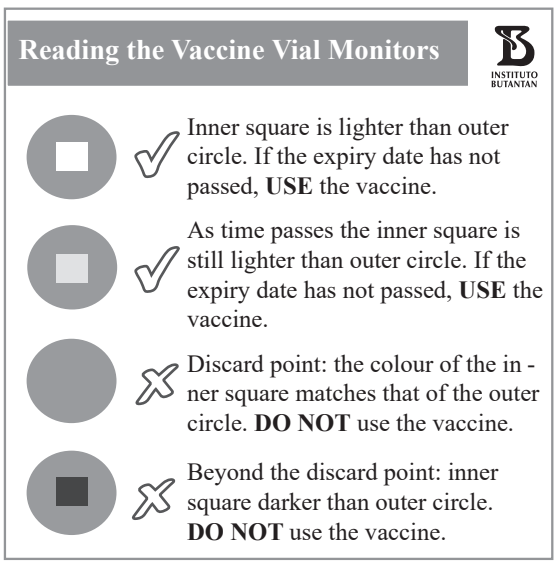
The trivalent influenza vaccine (split virion, inactivated) is available in packages of 20 x 5 mL (multidose vial - with 10 doses of 0.5 mL).
The vials are made of Type 1 glass. The container closure system for this presentation does not contain latex (natural rubber).

Marketing Authorization Holder:

INSTITUTO BUTANTAN – Av. Dr. Vital Brasil, 1500, Butantã, São Paulo/SP, Brazil.
This leaflet was last approved in 10/18/2021.

The Vaccine Vial Monitors (VVM) are on the cap of trivalent influenza vaccine (split virion, inactivated) supplied by INSTITUTO BUTANTAN. The color dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

Fig. The Vaccine Vial Monitor



The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the circle, then the vaccine can be used. As soon as the colour of the central square is the same colour as the circle or of a darker colour than the circle, then the vial should be discarded.