PUBLIC ASSESSMENT SUMMARY REPORT
SEASONAL TRIVALENT INFLUENZA VACCINE (SPLIT VIRION, INACTIVATED).
Instituto Butantan / Fundação Butantan (Brazil)

What is the trivalent influenza vaccine (split virion, inactivated)?

The vaccine is a slightly whitish, opalescent suspension for injection presented in a multidose vial.

Each dose of vaccine (0.5 mL) contains:

Active components and quantity per dose	
Influenza Virus A/H1N1 Strain, Split Virion, Inactivated	15 µg of HA antigen + overage*
Influenza Virus A/H3N2 Strain, Split Virion, Inactivated	15 µg of HA antigen + overage*
Influenza Virus B Strain (Victoria Lineage), Split Virion, Inactivated	15 µg of HA antigen + overage*
Excipients	
Thiomersal	2 µg/dose
Buffered saline solution †	Buffering agent and diluent

* 33,3% of overage.

† 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 µg of formaldehyde, traces of neomycin, octoxynol-9 and ovalbumin.

The seasonal trivalent influenza vaccine comes in a carton box containing 20 vials of vaccine. Each vaccine vial consists of 10 doses of 0.5 mL. The vaccine can be administered by an intramuscular or deep subcutaneous injection.

The vaccine is filled in a hydrolytic Type I glass vial. The vials closure system is complemented with a pharmaceutical grade stopper of bromobutyl, secured by a rigid lacquered aluminium crim cap.

The stability data submitted by the manufacturer supports a shelf life of 12 months when the vaccine is stored between 2°C to 8°C. The vaccine should be shipped and stored at this recommended temperature and it should not be frozen. The data provided support the use of VVM 7 and if required it will be part of the vaccine label.

Seasonal trivalent influenza vaccine (split virion, inactivated) is manufactured by Instituto Butantan / Fundação Butantan, Sao Paulo, Brazil.

What is trivalent influenza vaccine (split virion, inactivated) used for?

The vaccine is indicated for the active immunization of adults and children from 6 months of age for the prevention of influenza disease caused by the two influenza A virus subtypes and one influenza B virus types contained in the vaccine, as recommended by WHO (WHO position paper November 2012).

How is the trivalent influenza vaccine (split virion, inactivated) used?

The vaccine helps to protect you or your child against influenza (flu) which is a disease that can spread rapidly and is caused by different types of virus strains that can change every year. Due to this potential change in circulating strains on a yearly basis, as well as the duration of protection intended by the vaccine, vaccination is recommended every year.

It is intended to protect you or your child against the three strains of virus contained in the vaccine about 2 to 3 weeks after the injection. In addition, if you or your child are exposed to flu immediately before or after your vaccination, you or your child could still develop the illness as the incubation period for flu takes few days.

Adults receive one dose of 0.5 mL.

Children from 6 months to 8 years of age receive two 0.5 mL doses at interval of at least 4 weeks if they have not been previously vaccinated against flu. When they have been previously vaccinated, children should receive only one 0.5 mL dose.

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.

In children from 9 years to 17 years of age one 0.5 mL dose is administered.

The vaccine will not protect you or your child against the common cold, even though some of the symptoms are similar to flu.

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

The vaccine should be allowed to reach room temperature before use and should be shake gently before use.

Seasonal trivalent influenza vaccine (split virion, inactivated) should not be used if foreign particles are present in the suspension.

After first opening, the vaccine contained in the vial must be used within 28 days, according to the WHO vaccine open vial policy (as described in the WHO policy statement: Handling of multi dose vaccine vials after opening, WHO/IVB/14.07), and stored between 2°C and 8°C and protected from light.

For each dose withdrawn and for each patient, a new sterile syringe fitted with a new sterile needle is used. The vaccine is not to be mixed with other vaccines/products in the same syringe.

Between the different withdrawals and, in any case, within no more than 5 minutes after a dose is withdrawn, the vial should be put back in the refrigerator to keep the product at the temperature recommended by the manufacturer between 2°C and 8°C (never in the freezer).

An opened or partially used vial must be discarded immediately if:

- a sterile dose withdrawal has not been fully observed,
- there is any suspicion that the vial has been contaminated,
- there is visible sign of contamination, such as a change in the appearance or the presence of particles in suspension.

What are the vaccine characteristics?

Seasonal trivalent influenza vaccine (split virion, inactivated) is a freeze sensitive vaccine and must be stored as recommended by manufacturer between 2°C to 8°C. Therefore, it must not be frozen. Under these recommended storage conditions, the vaccine is stable for 12 months from the date of manufacture.

The vaccine contains thiomersal as a preservative.

Cold chain volume per dose is 4.08 cm^3/dose in the secondary carton of 20 vials.

Who is the regulatory authority responsible for its oversight vis a vis WHO?

The Brazilian Agência Nacional de Vigilância Sanitária (Anvisa) is the National Regulatory Authority (NRA) of record for the WHO prequalification procedure. The Marketing Authorization (MA) for the vaccine was issued by Anvisa on 13/02/2002. The agency is notified on annual basis on the update in the vaccine strains.

How has the trivalent influenza vaccine (split virion, inactivated) been studied from the clinical point of view?

To note in this section that the vaccine is the result of technology transfer from Sanofi Pasteur SA (France) concerning their vaccine Vaxigrip® which is a vaccine pre-qualified by WHO. Therefore, no pre-licensure studies were conducted with this vaccine prior to licensing in Brazil in 2013. However, as part of post licensure requirements, the Instituto Butantan conducted a safety and immunogenicity study of its annual Influenza vaccine for the following influenza seasons, 2013, 2014 and 2015.

Moreover, Instituto Butantan provided the study report of "A Phase 4 double-blind, randomized, non-inferiority trial, to examine the safety and immunogenicity of the Instituto Butantan Trivalent Seasonal Influenza Vaccine in comparison with the Sanofi Trivalent Seasonal Influenza Vaccine in Brazilian subjects." Approximately 624 healthy male and female (non-pregnant) adults, 18 to 69 years of age (at least 20% of the cohort is composed of subjects ≥ 60-69 years old) were recruited. Primary immunogenicity endpoint was to determine whether immunogenicity elicited by a single-dose of Instituto Butantan Trivalent Seasonal Influenza Vaccine is not inferior to that elicited by a single-dose of Sanofi Pasteur Trivalent Seasonal Influenza Vaccine in adults, including an elderly subgroup, measured by HI GMT for the three vaccine components 21 days post-immunization. The primary safety endpoint for this study was to describe the safety profile of Instituto Butantan Trivalent Seasonal Influenza Vaccine and Sanofi Pasteur Trivalent Seasonal Influenza Vaccine after a single dose in adult and elderly population. With this study results, Instituto Butantan has demonstrated in a blinded randomized study that the vaccine immunogenicity is non inferior to the Sanofi vaccine and the safety profiles of both vaccines were comparable.

Additionally, Instituto Butantan provided a report on an active pharmacovigilance study (FLU-05-IB) of the vaccine based on 2017 southern hemisphere strains. This was an observational prospective cohort study with the objective of identifying and evaluating adverse event following immunization among subjects vaccinated with the influenza vaccine during the national immunization campaign. Enrolled subjects vaccinated with Instituto Butantan influenza vaccine were actively followed-up for potential adverse events, both solicited and unsolicited, occurring 14 days after vaccination. Primary, secondary and exploratory endpoints were defined.

It is important to point out that because the study FLU-05-IB did not achieve the desired sample size for elderly and health care professionals, another study was conducted (FLU-06-IB) in the following influenza immunization campaign (2018) to achieve the sample size for these two groups.

The FLU-05-IB study started on 9 May 2017, a total of 533 participants were included by the end of the study, and the final participant contact was made on September 2017. The FLU-06-IB study started on 22 May 2018. A total of 403 participants were included by the end of the study, and the final participant contact was made on August 2018.

Study results confirm the acceptable safety profile of the Trivalent Influenza Vaccine (split virion, inactivated) produced by Instituto Butantan, in healthy individuals of all ages and at-risk populations (i.e. elderly, health care workers, children, pregnant women and post-partum women). No serious adverse events were reported. No neurological signs and/or symptoms that could be associated with Guillain-Barré Syndrome were reported up to 42 days post immunization. Most of the solicited adverse reactions reported for all participants were Grades 1 and 2, lasting on average less than a day. Pain at the vaccine administration site was the most frequently reported local, solicited adverse reaction (46.6%). The most frequent solicited systemic adverse reaction reported was headache (22.5%). The majority of the unsolicited adverse reactions reported in the study were also Grades 1 and 2. The most frequent unsolicited adverse reactions reported in the study was musculoskeletal pain (3%). This reaction was classified as unexpected and an investigation was conducted to confirm it upon completion of the study. The investigation led to the conclusion that there was in fact myalgia. Overall, Butantan vaccine demonstrated a similar safety profile as Vaxigrip®, according to a review article summarizing almost 50 years of usage of the latter. Both Vaxigrip® adverse reactions spontaneously reported or reported during clinical studies were also mild to moderate and more common in adults than in the elderly; pain at the administration site was the most frequently reported local adverse reaction. Fever and irritability were frequently reported among children, and headache and myalgia among the adult groups.

Other information about evaluation of Trivalent Influenza Vaccine (split virion, inactivated):

The decision to prequalified the trivalent influenza vaccine (split virion, inactivated) manufactured by Instituto Butantan was supported by the evaluation of the prequalification dossier and the review of the appropriate information submitted to WHO, the testing results of vaccine samples conducted by WHO independent laboratories along with the information shared by the Brazilian Agência Nacional de Vigilância Sanitária (Anvisa) on the regulatory status of the company.

The vaccine prequalification dossier was submitted in a Product Summary File (PSF) format. The vaccine meets WHO WHO_TRS_927, Annex 3 “Recommendations for the production and control of influenza vaccine (inactivated)” and a WHO position paper on influenza. In addition, the vaccine was found in compliance with WHO programmatic suitability, stability data (with respect to VVM assignment) and UN specific labelling requirement.

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