ADACEL®-POLIO

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine

Intramuscular injection

Suspension for injection

DESCRIPTION

ADACEL®-POLIO (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine) is a sterile, uniform, cloudy, white suspension of tetanus and diphtheria toxoids and acellular pertussis vaccine adsorbed separately on aluminum phosphate, combined with inactivated poliomyelitis vaccine (vero cell origin) types 1, 2 and 3, and suspended in water for injection. The acellular pertussis vaccine is composed of five purified pertussis antigens (PT, FHA, PRN and FIM).

INDICATIONS AND CLINICAL USE

ADACEL®-POLIO is indicated for active immunization against diphtheria, tetanus, pertussis and poliomyelitis in adults, adolescents and children aged 4 years and older as a booster following primary immunization.

ADACEL®-POLIO is not indicated for primary immunization.

Passive protection against pertussis in early infancy following maternal immunization during pregnancy (see section WARNINGS AND PRECAUTIONS, Special Populations-Pregnant Women and DOSAGE AND ADMINISTRATION)

ADACEL®-POLIO should be used in accordance with official recommendations.

Persons who have had tetanus, diphtheria or pertussis should still be immunized since these clinical infections do not always confer immunity. Human Immunodeficiency Virus (HIV)-infected persons, both asymptomatic and symptomatic, should be immunized against tetanus, diphtheria and pertussis according to standard schedules.

ADACEL®-POLIO is not to be used for the treatment of disease caused by *Bordetella pertussis, Corynebacterium diphtheria, Clostridium tetani* or poliomyelitis infections.

Tetanus Prophylaxis in Wound Management

The need for active immunization with a tetanus toxoid-containing preparation (such as Td Adsorbed vaccine, ADACEL® or ADACEL®-POLIO) with or without passive immunization with Tetanus Immune Globulin, depends on both the condition of the wound and the patient's vaccination history. (See DOSAGE AND ADMINISTRATION)

CONTRAINDICATIONS

Hypersensitivity

Known systemic hypersensitivity reaction to any component of ADACEL®-POLIO or a life-threatening reaction after previous administration of the vaccine or a vaccine containing one or more of the same components are contraindications to vaccination. Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such persons may be referred to an allergist for evaluation if further immunizations are considered.

Acute Neurological Disorders

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including ADACEL®-POLIO.

WARNINGS AND PRECAUTIONS

General

Before administration of ADACEL®-POLIO, health-care providers should inform the recipient or parent or guardian of the recipient of the benefits and risks of immunization, inquire about the recent health status of the patient to be immunized, review the patient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization and comply with any local requirements regarding information to be provided to the patient/guardian before immunization.

It is extremely important that the recipient, parent or guardian be questioned concerning any signs or symptoms of an adverse reaction after a previous dose of vaccine. (See Tetanus Prophylaxis in Wound Management

The need for active immunization with a tetanus toxoid-containing preparation (such as Td Adsorbed vaccine, ADACEL® or ADACEL®-POLIO) with or without passive immunization with Tetanus Immune Globulin, depends on both the condition of the wound and the patient's vaccination history. (See DOSAGE AND ADMINISTRATION)

CONTRAINDICATIONS and ADVERSE REACTIONS.)

Syncope (fainting) has been reported following vaccination with ADACEL®-POLIO. Procedures should be in place to prevent falling injury and manage syncopal reactions.

The rates and severity of adverse events in recipients of tetanus toxoid are influenced by the number of prior doses and level of pre-existing antitoxins.

As with any vaccine, ADACEL®-POLIO may not protect 100% of vaccinated persons.

Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born to women vaccinated with ADACEL®-POLIO during pregnancy. The clinical relevance of this observation is unknown.

Administration Route Related Precautions: Do not administer ADACEL®-POLIO by intravascular injection: ensure that the needle does not penetrate a blood vessel.

Intradermal or subcutaneous routes of administration are not to be utilized.

ADACEL®-POLIO should not be administered into the buttocks.

Febrile and Acute Disease: Vaccination should be postponed in cases of an acute or febrile disease. However, a disease with low-grade fever should not usually be a reason to postpone vaccination.

Hematologic

Because any intramuscular injection can cause an injection site hematoma in persons with any bleeding disorders, such as haemophilia or thrombocytopenia, or in persons on anticoagulant therapy, intramuscular injections with ADACEL®-POLIO should not be administered to such persons unless the potential benefits outweigh the risk of administration. If the decision is made to administer any product by intramuscular injection to such persons, it should be given with caution, with steps taken to avoid the risk of hematoma formation following injection.

Immune

The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Hypersensitivity reactions may occur following the use of ADACEL®-POLIO even in persons with no prior history of hypersensitivity to the product components.

As with all other products, epinephrine hydrochloride solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.

Immunocompromised persons (whether from disease or treatment) may not achieve the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment. Nevertheless, vaccination of persons with chronic immunodeficiency, such as HIV infection, is recommended even if the immune response might be limited.

Neurologic

ADACEL®-POLIO should not be administered to individuals with progressive neurological disorder, uncontrolled epilepsy, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized.

A review by the US Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give ADACEL®-POLIO or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

Special Populations

Pregnant Women

No teratogenic effect of vaccines containing diphtheria or tetanus toxoids, or inactivated poliovirus has been observed following use in pregnant women.

Safety data from 4 randomized controlled trials (310 pregnancy outcomes), 2 prospective observational studies (2670 pregnancy outcomes), 4 retrospective observational studies (81,701 pregnancy outcomes), and from passive surveillance of women who received ADACEL®-POLIO or ADACEL® (Tdap component of ADACEL®-POLIO; containing the same amounts of diphtheria, tetanus and pertussis antigens) during the 2nd or 3rd trimester have shown no vaccine-related adverse effect on pregnancy or on the health of the fetus/newborn child. As with other inactivated vaccines, it is not expected that vaccination with ADACEL®-POLIO during any trimester would harm the fetus. The benefits versus the risks of administering ADACEL®-POLIO during pregnancy should be evaluated.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Limited clinical data have shown there is interference with the immune response to other antigens (i.e. diphtheria, tetanus, polio, pneumococcal, meningococcal) in infants born to women vaccinated with ADACEL®-POLIO during pregnancy. However, in most of the cases, the antibody concentrations remain above the thresholds established as protective. The clinical relevance of this observation is unknown.

Nursing Women

The effect of administration of ADACEL®-POLIO during lactation has not been assessed. As ADACEL®-POLIO is inactivated, any risk to the mother or the infant is improbable. However, the effect on breast-fed infants of the administration of ADACEL®-POLIO to their mothers has not been studied. The risks and benefits of vaccination should be assessed before making the decision to immunize a nursing woman.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

The safety of ADACEL®-POLIO has been evaluated in a total of 1,636 participants who received a single dose of ADACEL®-POLIO in 7 clinical trials (644 children 3 to 7 years of age, 992 adolescents and adults 11 to 60 years of age). Pain was the most common injection site reaction in all age groups. Most injection site reactions occurred within 3 days following vaccination. The most frequent systemic reaction was headache in adolescents and adults and tiredness in children. These reactions were usually transient and of mild to moderate intensity.

Table 1 presents the frequencies of the solicited injection site and systemic adverse events reported in 3 UK clinical trials in which children previously primed with 3 doses of PEDIACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine and Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] or a whole-cell pertussis combination vaccine, received a pre-school booster dose of ADACEL®-POLIO at 3 to 5 years of age. In addition, adverse events of irritability (7.3%), injection site bruising (3.3%), injection site pruritus (2.7%) and dermatitis (1.3%) were reported within 7 days of vaccination in two of these studies.

In clinical trials in children ADACEL®-POLIO showed a comparable safety profile to that of ADACEL® [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed]. Therefore, the safety of ADACEL®-POLIO, in particular for use as a 4 to 6 years-old booster dose is further supported by a study conducted with ADACEL® in 298 children.

The frequency of the solicited injection site and systemic adverse events reported in a Canadian clinical trial in adolescents and adults are also presented in Table 1.

Table 1: Frequency (%) of Solicited Reactions Observed in Clinical Trials in Children, Adolescents and Adults, Following a Single Booster Dose of ADACEL®-POLIO

Solicited Reactions	Children 3 to 5 Years of Age* (N = 307)	Adolescents 12 to 18 Years of Age† (N = 350)	Adults 19 to 60 Years of Age† (N = 366)
Injection Site Reactions			
Pain	46.5 – 71.3	88.3	86.3
Swelling	20.4 – 34.0	21.2	16.7
Redness	35.7 – 48.7	17.5	23.0
Systemic Reactions			
Fever‡	7.0 – 12.7	14.2	2.7
Headache	N.S.	41.3	37.7
Nausea	N.S.	17.5	14.5
Diarrhea	7.6 – 10.0	5.4	15.8
Vomiting	2.5 – 6.7	3.2	2.5
Body Ache	N.S.	26.1	24.0
Sore or Swollen Joints	1.3	11.2	11.2
Tiredness	35.7 – 52.7	37.2	29.8
Chills	N.S.	17.5	11.2
Rash	7.0 – 8.7	N.S.	N.S.

* Adverse reactions reported within 7 days of vaccination. Range of frequencies across 3 UK studies.

† Adverse reactions reported within 14 days of vaccination

‡ Fever was defined as temperature ≥37.5°C in children, ≥38.0°C in adolescents and adults. Fever was solicited up to 7 days post-vaccination in children, up to 72 hours in adolescents and adults.

N.S. Not solicited

Post-Market Adverse Drug Reactions

The following additional adverse events have been spontaneously reported during the post-marketing use of ADACEL®-POLIO. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Blood and Lymphatic Disorders

Lymphadenopathy

Immune System Disorders

Anaphylactic reactions, such as urticaria, face edema and dyspnea

Nervous System Disorders

Convulsions, vasovagal syncope, Guillain-Barré syndrome, facial palsy, myelitis, brachial neuritis, transient paresthesia/ hypoesthesia of vaccinated limb, dizziness

Musculoskeletal and Connective Tissue Disorders

Pain in vaccinated limb

Gastrointestinal Disorders

Abdominal pain

General Disorders and Administration Site Conditions

Extensive limb swelling, which may extend from the injection site beyond one or both joints and is frequently associated with erythema, and sometimes with blisters, has been reported following administration of ADACEL®-POLIO. The majority of these reactions appeared within 48 hours of vaccination and spontaneously resolved over an average of 4 days without sequelae. The risk appears to be dependent on the number of prior doses of d/DTaP vaccine, with a greater risk following the 4^{th} and 5^{th} doses.

Malaise, pallor, injection site induration

DRUG INTERACTIONS

Vaccine-Drug Interactions

Immunosuppressive treatments may interfere with the development of the expected immune response. (See WARNINGS AND PRECAUTIONS.)

Concomitant Vaccine Administration

ADACEL®-POLIO may be administered concurrently with a dose of hepatitis B vaccine. Supportive data from a study conducted with ADACEL® suggests that ADACEL®-POLIO may be used concomitantly with trivalent influenza vaccine. ADACEL®-POLIO has been safely administered concomitantly with measles-mumps-rubella vaccine in non-controlled clinical studies in children 3 to 5 years of age. Data are not available on concomitant use of ADACEL®-POLIO and varicella vaccine.

Administering the most widely used live and inactivated vaccines during the same patient visit has produced seroconversion rates and rates of adverse reactions similar to those observed when the vaccines are administered separately. Vaccines administered concomitantly should be given using separate syringes at separate sites. Simultaneous administration is suggested, particularly when there is concern that a person may not return for subsequent vaccination.

ADACEL®-POLIO should not be mixed in the same syringe with other parenterals.

DOSAGE AND ADMINISTRATION

Recommended Dose

ADACEL®-POLIO should be administered as a single injection of 1 dose (0.5 mL) by the intramuscular route. The preferred site is the deltoid muscle.

ADACEL®- POLIO may be administered to pregnant women during the second or third trimester to provide passive protection of infants against pertussis (see sections INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS and Special Populations-Pregnant Women).

Fractional doses (doses <0.5 mL) should not be given. The effect of fractional doses on safety and efficacy has not been determined.

The use of ADACEL-POLIO® in management of tetanus-prone wounds should follow local recommendations.

History of tetanus vaccination	Time since last dose	Type of wound	Tdap, DTap combinations, DT, Tdap (as appropriate)	Tetanus immunoglobulin* (TIG)
≥ 3 doses	<5 yrs	Clean minor wounds	No	No
		All other wounds †	No	No#
≥ 3 doses	5-10 yrs	Clean minor wounds	No	No
		All other wounds †	Yes	No#
≥ 3 doses	>10 yrs	Clean minor wounds	Yes	No
		All other wounds †	Yes	No#
< 3 doses or uncertain§		Clean minor wounds	Yes	No
		All other wounds †	Yes	Yes

* The recommended dose for TIG is 250 IU, given by IM injection, as soon as practicable after the injury. If more than 24 hours have elapsed, 500 IU should be given. Because of its viscosity, TIG should be given to adults using a 21 gauge needle. For children, it can be given slowly using a 23 gauge needle.

† All wounds other than clean minor wounds should be considered "tetanus-prone"

Individuals with humoral immune deficiency (including HIV infected persons who have immunodeficiency) should be given TIG if they have received a tetanus-prone injury, regardless of the time since their last dose of tetanus-containing vaccine.

§ Persons who have no documented history of a primary vaccination course (3 doses) with a tetanus toxoid-containing vaccine should receive all missing doses and must receive TIG.

For adults who have not previously received a dose of acellular pertussis vaccine, a single Tetanus-diphtheria (Td) booster dose should be replaced by a combine tetanus-diphtheria-acelluar pertussis vaccine (Tdap).

Administration

Inspect for extraneous particulate matter and/or discolouration before use. (See DESCRIPTION.) If these conditions exist, the product should be discarded.

Shake the syringe well until a uniform, cloudy, suspension results. When administering a dose from a stoppered vial, do not remove either the stopper or the metal seal holding it in place. Use a separate sterile needle and syringe, or a sterile disposable unit for each individual patient to prevent disease transmission. Needles should not be recapped but should be disposed of according to biohazard waste guidelines.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. Administer the total volume of 0.5 mL **intramuscularly** (IM). The preferred site of injection is the deltoid muscle.

ACTION AND CLINICAL PHARMACOLOGY

Tetanus and Diphtheria: Protection against disease attributable to *C. tetani* is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay, is considered the minimum protective level. One month after a single booster dose of ADACEL®-POLIO, seroprotective tetanus antitoxin levels were achieved in 100% of adults and adolescents, and at least 100% of children 3.5 to 4.1 years of age.

Protection against disease attributable to *C. diphtheriae* is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective for diphtheria. 83.8% of adults, 97.1% of adolescents and at least 97.6% of children 3.5 to 4.1 years of age achieved a seroprotective antitoxin level of 0.1 IU/mL against diphtheria.

Pertussis: Pertussis (whooping cough) is a respiratory disease caused by *B. pertussis*. This Gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined. The mechanism of protection from *B. pertussis* disease is not well understood. However, in a clinical trial in Sweden (Sweden I Efficacy Trial) using TRIPACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed], the same pertussis components as present in ADACEL®-POLIO (i.e., PT, FHA, PRN and FIM) have been shown to prevent pertussis in infants with a protective efficacy of 85.2% using the World Health Organization (WHO) case definition (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiological link to a confirmed case). In the same study, the protective efficacy against mild disease was 77.9%.

Minimum serum antibody levels to specific pertussis vaccine components that confer protection against the development of clinical pertussis have not been established. Nevertheless, a number of studies have demonstrated a correlation between the presence of serum antibody responses to pertussis vaccine components and protection against clinical disease. The acellular pertussis formulations of ADACEL®-POLIO and ADACEL® compared to TRIPACEL® differ only in the amount of PT (2.5 µg in ADACEL®-POLIO and ADACEL® versus 10 µg in TRIPACEL®) and the amount of diphtheria toxoid (2 Lf in ADACEL®-POLIO and ADACEL® versus 15 Lf in TRIPACEL®). Furthermore, the IPV antigens present in ADACEL®- POLIO® are not included in the formulation of TRIPACEL®.

The efficacy of ADACEL®-POLIO is based on a comparison of pertussis antibody levels achieved in ADACEL®-POLIO recipients with those measured with TRIPACEL® in the Sweden I Efficacy Trial. In particular, ADACEL®-POLIO was demonstrated, both in children and in adolescents and adults, to elicit antibody levels against pertussis antigens, which were consistently higher that those found to be protective in the Sweden I Efficacy Trial. In addition, in a clinical study with ADACEL® among Canadian 4 to 6 year-olds, it was demonstrated that, in the context of the Canadian immunization schedule, the pertussis antigens formulation of ADACEL®-POLIO also elicited serum antibody levels that were consistently higher than those measured in the Sweden I Efficacy Trial.

Poliomyelitis: Inactivated poliomyelitis vaccine induces the production of detectable levels of neutralizing antibodies against each type of poliovirus. The detection of type-specific neutralizing antibodies has been correlated with protection. In all clinical trials, 99.0% to 100% of vaccinees in all age groups achieved seroprotective levels (≥1:8 dilution) of anti-poliovirus antibodies for all three types.

Duration of Effect

Long-term follow-up of serum antibody levels in adolescents and adults who received a single dose of ADACEL®-POLIO shows that protective levels for tetanus antitoxin (≥0.01 IU/mL) and diphtheria antitoxin (≥0.01 IU/mL) persist in 100% and at least 79.2% of participants, respectively, after at least 5 years. Protective levels of anti-poliovirus antibodies (≥1:8) persist in 98.2% to 100.0% of both adolescents and adults after 5 years. While protective levels against pertussis have not yet been clearly defined, pertussis antibody levels remain several-fold higher than pre-immunization levels after 5 years.

Long-term follow-up of serum antibody levels in children who received a single dose of ADACEL®-POLIO at 3.5 to 5 years of age shows that protective levels for tetanus antitoxin (≥0.01 IU/mL) and diphtheria antitoxin (≥0.01 IU/mL) persist in 100.0% of participants, 3 years after immunization. Protective levels of anti-poliovirus antibodies (≥1:8) persist in 97.9 to 100.0% of participants after 3 years. While protective levels against pertussis have not yet been clearly defined, after 3 years, pertussis antibody levels remain higher than pre-immunization levels. (25)

According to NACI, tetanus and diphtheria toxoid boosters are recommended every 10 years, however, the optimal interval for administering subsequent booster doses with ADACEL®-POLIO has not been determined. Nevertheless, a clinical study conducted with ADACEL® demonstrated that the incidence and severity of adverse events reported after administration of ADACEL® as early as 2 years after the last dose of tetanus and diphtheria vaccine were similar to those observed after administration at greater time intervals, up to 10 years.

Passive protection of neonates and infants against pertussis

Based on findings from multiple studies of ADACEL®-POLIO and ADACEL® administered to pregnant women primarily during the 2nd or 3rd trimester of gestation:

- Pertussis antibody responses in pregnant women are generally similar to those in non-pregnant women.
- Maternal antibody directed against pertussis antigens persists for 2 to 4 months after birth and may be associated with blunting of the infant immune response to active immunization against pertussis (see section WARNING AND PRECAUTIONS).
- The effectiveness of maternal immunization against pertussis in the first 3 months of life has been estimated to be >90%.

Table 5: Vaccine effectiveness (VE) against pertussis disease in young infants born to mothers vaccinated during pregnancy with ADACEL®-POLIO and ADACEL® in 3 retrospective studies.

Location	Vaccine	VE (95% CI)	VE estimation method	Infant follow-up period
UK	ADACEL®-POLIO	93% (81, 97)	unmatched case-control	3 months
US	ADACEL®*	91.4% (19.5, 99.1)	cohort regression model	2 months
UK	ADACEL®-POLIO	93% (89, 95)	screening (case-coverage)	3 months

* Over 80% of Tdap used in study

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F). **Do Not Freeze**. Discard product if exposed to freezing.

Do not use after expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

ADACEL®-POLIO is supplied as a sterile, uniform, cloudy, white suspension in a prefilled syringe.

Composition

Each dose (0.5 mL) is formulated to contain:

Active Ingredients

Tetanus Toxoid	Not less than 20 International Units (5 Lf)
Diphtheria Toxoid	Not less than 2 International Units (2 Lf)
Acellular Pertussis:	
Pertussis Toxoid (PT)	2.5 µg
Filamentous Haemagglutinin (FHA)	5 µg
Pertactin (PRN)	3 µg
Fimbriae Types 2 and 3 (FIM)	5 µg
Inactivated Poliomyelitis Vaccine	
Type 1 (Mahoney)	40 D-antigen units*
Type 2 (MEF-1)	8 D-antigen units*
Type 3 (Saukett)	32 D-antigen units*

* or the equivalent antigen quantity, determined by suitable immunochemical method

Other Ingredients

Excipients

Aluminum Phosphate (adjuvant)	1.5 mg
2-phenoxyethanol	0.6% v/v
Polysorbate 80	<5 µg
Water for Injection	q.s. 0.5 mL

Manufacturing Process Residuals

Bovine serum albumin, formaldehyde, glutaraldehyde, streptomycin, neomycin and polymyxin B are present in trace amounts.

Packaging

ADACEL®-POLIO is presented as a suspension for injection in pre-filled syringes (0.5 mL).

Manufactured by:

SANOFI PASTEUR

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