NEW ZEALAND DATA SHEET

Name of the Medicinal Product

MENITORIX®

Haemophilus type b and *Neisseria meningitidis* group C conjugate vaccine

Presentation

MENITORIX is presented as a powder and diluent for reconstitution for intramuscular injection.

Each 0.5ml dose of the reconstituted vaccine contains 5 micrograms of *Haemophilus* type b polysaccharide (polyribosylribitol phosphate) conjugated to 12.5 micrograms of tetanus toxoid as a carrier protein and 5 micrograms of *Neisseria meningitidis* serogroup C (strain C11) polysaccharide conjugated to 5 micrograms of tetanus toxoid as a carrier protein.

Clinical Particulars

Therapeutic indications

MENITORIX is indicated for the prevention of invasive diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC).

Posology and method of administration

Primary vaccination in infants from 6 weeks up to 12 months of age:

Three doses, each of 0.5 ml, should be given with an interval of at least 1 month between doses.

Booster vaccination of children primed in infancy with Hib and MenC conjugate vaccines:

After primary vaccination against Hib and MenC in infancy, a booster dose is recommended to ensure long-term protection. The booster dose should be administered from the age of 12 months onwards and before the age of 2 years.

A single (0.5 ml) dose of MENITORIX may be used to boost immunity to Hib and MenC in children who have previously completed a primary immunisation series with MENITORIX or with other Hib or MenC conjugate vaccines. The timing of the booster dose of MENITORIX should be in accordance with available official recommendations and would usually be given from the age of 12 months onwards and at least 6 months after the last priming dose. The need for booster doses in subjects primed with a single dose of MenC conjugate (i.e. aged 12 months or more when first immunised) has not been established.

Vaccination of children primed in infancy with Hib but not with MenC conjugate vaccines:

A single (0.5ml) dose of MENITORIX may be used to elicit immunity against MenC and to boost immunity to Hib. The timing of the dose should be in accordance with available

official recommendations and should usually be from the age of 12 months onwards and before the age of 2 years.

Method of administration

MENITORIX is for intramuscular injection only, preferably in the anterolateral thigh region. In children 12 to 24 months of age, the vaccine may be administered in the deltoid region. *(see also sections Warnings and Precautions and Interactions)*

Contraindications

Hypersensitivity to the active substances, including tetanus toxoid, or to any of the excipients (*see section Pharmaceutical Particulars – List of excipients*).

Hypersensitivity reaction after previous administration of MENITORIX.

Special warnings and special precautions for use

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.

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

As with other vaccines, the administration of MENITORIX should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

The vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder. No data are available on subcutaneous administration of MENITORIX, therefore the possibility of any toxicity or reduced efficacy that might occur with this route of administration is unknown.

MENITORIX will only confer protection against *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroup C.

As for any vaccine, MENITORIX may not completely protect against the infections it is intended to prevent in every vaccinated individual.

No data are available on the use of MENITORIX in immunodeficient subjects. In individuals with impaired immune responsiveness (whether due to the use of immunosuppressive therapy, a genetic defect, human immunodeficiency virus (HIV) infection, or other causes) a protective immune response to Hib and MenC conjugate vaccines may not be obtained. Individuals with complement deficiencies and individuals with functional or anatomical asplenia may mount an immune response to Hib and MenC conjugate vaccines; however the degree of protection that would be afforded is unknown.

There are no data available on the use of MENITORIX in infants who were born prematurely. Therefore the degree of protection that would be afforded is unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48 to 72 hours should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Although symptoms of meningism such as neck pain/stiffness or photophobia have been reported following administration of other MenC conjugate vaccines, there is no evidence that MenC conjugate vaccines cause meningitis. Clinical alertness to the possibility of co-incidental meningitis should be maintained.

Immunisation with this vaccine does not substitute for routine tetanus immunisation.

MENITORIX should under no circumstances be administered intravascularly or intradermally.

Since the Hib capsular polysaccharide antigen is excreted in the urine a false positive urine test for Hib infection can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Interaction with other medicinal products and other forms of interaction

MENITORIX must not be mixed with any other vaccine in the same syringe.

Separate injection sites should be used if more than one vaccine is being administered.

MENITORIX can be given concomitantly with any of the following monovalent or combination vaccines: Diphtheria (D) – Tetanus (T) – acellular Pertussis (aP) – hepatitis B vaccine (HBV) – inactivated polio vaccines (IPV), Measles-Mumps-Rubella (MMR) vaccines and pneumococcal conjugate vaccines. Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected.

Care should be taken to ensure that MENITORIX is not administered concurrently with another vaccine containing either *Haemophilus influenza*e b or meningococcal C vaccine.

Use during pregnancy and lactation

As MENITORIX is not intended for use in adults, information on the safety of the vaccine when used during pregnancy is not available.

As MENITORIX is not intended for use in adults, information on the safety of the vaccine when used during lactation is not available.

Effects on ability to drive and use machines

Not applicable.

Undesirable effects

In clinical studies, MENITORIX was administered as a 3 or 2-dose primary series in infants (N=2,452) or as a booster (N=2,109) dose in the second year of life. Co-administered vaccines in studies in infants included, a DTPa-HBV-IPV vaccine or a DTPa-IPV vaccine or a DTPa-HBV-IPV vaccine and pneumococcal conjugate vaccine (10-valent, Synflorix® or 7-valent). When MENITORIX was administered as a booster dose, a DTPa-HBV-IPV vaccine or a MMR vaccine or a DTPa containing vaccine and pneumococcal conjugate vaccine (10-valent, Synflorix® or 7-valent) was co-administered in some studies.

In another clinical study, MENITORIX was administered as a single dose to more than 300 toddlers (between 12 and 24 months of age) who had been primed in infancy with Hib but not with MenC conjugates. A dose of MMR vaccine was administered concomitantly.

Adverse reactions occurring during these studies were mostly reported within 48 hours following vaccination. The majority of these reactions were of mild to moderate severity and resolved during the follow-up period. There was no evidence that the reactions other than injection site reactions were related to MENITORIX rather than the concomitant vaccine.

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency as follows.

Frequencies per dose are defined as follows:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100
Rare: ≥ 1/10000 to < 1/1000
Very rare: < 1/10000

<u>Psychiatric disorders:</u>
Very common: irritability
Uncommon: crying
Rare: insomnia

<u>Nervous system disorders:</u>
Very common: drowsiness

<u>Gastrointestinal disorders:</u>
Very common: loss of appetite
Uncommon: diarrhoea, vomiting
Rare: abdominal pain

<u>Skin and subcutaneous tissue disorders:</u>
Uncommon: dermatitis atopic, rash

<u>General disorders and administration site conditions:</u>
Very common: injection site reactions (pain, redness and swelling), fever (rectal ≥ 38°C)
Common: injection site reactions (including induration and nodule)
Uncommon: fever (rectal > 39.5°C)
Rare: malaise

Post Marketing Data

Immune system disorders:
Very rare: anaphylaxis

Nervous system disorders:
Very rare: febrile convulsions

Other possible side effects:
The following have not been reported in association with administration of MENITORIX but have occurred very rarely during routine use of licensed meningococcal group C conjugate vaccines:

Severe skin reactions, collapse or shock-like state (hypotonic-hyporesponsiveness episode), faints, seizures in patients with pre-existing seizure disorders, hypoaesthesia, paraesthesia, relapse of nephrotic syndrome, arthralgia, petechiae and/or purpura.

Overdose
Insufficient data are available.

Pharmacological Properties

Mechanism of Action
MENITORIX confers immunization against *Haemophilus influenzae* type b and *Neisseria meningitides* serogroup C by inducing T-cell dependent antisaccharide antibody response leading to the establishment of immunological memory.

Pharmacodynamic Effects
Immunogenicity against *Haemophilus influenzae* type b was evaluated by measuring anti-polyribosylribitol phosphate antibodies (anti-PRP) with an enzyme-linked immunosorbent assay (ELISA). Immunogenicity against *Neisseria meningitidis* serogroup C was evaluated by a serum bactericidal activity assay (SBA-MenC).

The correlates indicative of protection in the MENITORIX development program were an anti-PRP antibody concentration of 0.15μg/mL and a SBA-MenC antibody titre of 1:8, which are very widely accepted.

Study Hib-MenC-TT-016 was a pivotal clinical trial conducted in Australia and according to the National Immunisation Program, to evaluate the use of MENITORIX as a single dose in children primed in infancy with a Hib vaccine but not with a MenC vaccine.

Primary vaccination course:

The antibody responses at one month after two doses and after completion of a 3-dose primary vaccination course of MENITORIX were as follows:

Table 1: Antibody response of Menitorix co-administered with DTPa-IPV or DTPa-HBV-IPV vaccines with or without co-administration with a pneumococcal conjugate vaccine

Antigen	Response	Antibody response of Menitorix*			
		2-3-4 month schedule		2-4-6 month schedule	
		After two doses[1]	After three doses‡	After two doses[2]	After three doses
Anti-PRP	% ≥0.15μg/ml (n/N)	96.8% (90/93)	100.0% (335/335)	94.1% (430/457)	99.3% (450/453)
	% ≥1μg/ml (n/N)	76.3% (71/93)	97.3% (326/335)	67.2% (307/457)	96.9% (439/453)
	GMC (μg/ml) (N)	3.40 (93)	11.18 (335)	2.063 (457)	12.412 (453)
SBA-MenC	% ≥1:8 (n/N)	100.0% (93/93)	98.8% (326/330)	98.4% (438/445)	99.7% (367/368)
	% ≥1:32 (n/N)	98.9% (92/93)	97.9% (323/330)	97.5% (434/445)	99.7% (367/368)
	≥1:128 (n/N)	98.9% (92/93)	92.4% (305/330)	90.6% (403/445)	97.0% (357/368)
	GMT (N)	679.6 (93)	685.5 (330)	581.0 (445)	1735.0

N= number of subjects with available results
n/%= number/percentage of subjects with titre within pre-specified range
[1]Bloodsampling one month after the second dose
[2]Bloodsampling two months after the second dose
PRP= polyribosylribitol phosphate
SBA-MenC= functional anti-meningococcal serogroup C activity
GMC or GMT= geometric mean antibody concentration or titre
*= co-administered with DTPa-IPV or DTPa-HBV-IPV vaccines with or without co-administration with a pneumococcal conjugate vaccine (10-valent, Synflorix®, 7-valent, Prevenar)
‡= subjects ≤18 weeks of age at time of third Menitorix dose

Antibody persistence after a 3 dose primary vaccination course has been demonstrated for Hib in -five clinical trials with subjects aged 11-18 months and primed with MENITORIX in infancy at 2-3-4 or 2-4-6 months of age. Following completion of the 3 dose primary series with MENITORIX, 97.0% of the subjects (847/873) had anti-PRP titers ≥ 0.15 μg/ml and 84.9% of the subjects had SBA-MenC titers ≥ 1:8 (595/701).

All subjects responded immunologically to a challenge dose of 10 μg of unconjugated serogroup C meningococcal polysaccharide with a thirty-three-fold increase in SBA titres demonstrating the immune memory induced by the primary vaccination course.

Booster vaccination:

In six clinical trials booster vaccination was given at age 12 to 15 months. The antibody responses one month after administration of a booster dose of MENITORIX were as follows:

Table 2: Antibody response 1 month after administration of a booster dose of Menitorix

Booster response of M

Antigen	Response	Primary vaccination history		
		Subjects primed with 3 doses of Menitorix*[1]	Subjects primed with 2 doses of NeisVac-C**[2]	Subjects primed with 3 doses of MenC-CRM$_{197}$**[2]
Anti-PRP	%≥0.15 μg/ml (n/N)	100.0% (780/780)	100.0% (165/165)	100.0% (305/305)
	%≥1 μg/ml (n/N)	100.00% (780/780)	98.8% (163/165)	99.0% (302/305)
	GMC (μg/ml) (N)	70.142 (780)	77.154 (165)	38.178 (305)
SBA-MenC	% ≥1:8 (n/N)	99.5% (621/624)	99.4% (166/167)	97.7% (297/304)
	% ≥1:32 (n/N)	99.4% (620/624)	99.4% (166/167)	96.4% (293/304)
	%≥1:128 (n/N)	98.2% (613/624)	99.4% (166/167)	89.1% (271/304)
	GMT (n/N)	3486.4 (624)	11710.5 (167)	575.1 (304)

N= number of subjects with available results
n/%=number/percentage of subjects with titre within pre-specified range
PRP= polyribosylribitol phosphate
SBA-MenC= functional anti-meningococcal serogroup C activity
GMC or GMT= geometric mean antibody concentration or titre
*[1]= co-administered with DTPa-IPV or with DTPa-HBV-IPV with or without co-administration with a pneumococcal conjugate vaccine (10-valent, Synflorix® or 7-valent, Prevenar)
**[2]= co-administered with DTPa-Hib-TT containing vaccines

Immunogenicity of a single dose in MenC-unprimed toddlers

A study was carried out in Australia in toddlers primed in infancy with a Hib conjugate vaccine but not with a Men C conjugate vaccine. These participants had received Hib vaccine either as 2 doses of a Hib-outer membrane protein [Hib-OMP] containing vaccine or as 3 doses of of Hib-TT (as part of a combination vaccine with diphtheria, tetanus, acellular pertussis). This study investigated the non-inferiority of one dose of MENITORIX compared with co-administration of Hib-TT amd MenC-CRM vaccines. Both groups also received measles-mumps-rubella vaccine, Priorix®.

The data in Table 3 demonstrate non-inferiority of MENITORIX to the comparator (Hib+MenC) based on the pre-specified non-inferiority in terms of percentages of subjects with SBA-MenC titres ≥1:8 and percentages of subjects with anti-PRP antibody concentrations ≥0.15μg/mL.

Table 3: Difference between the Menitorix group and the Hib+MenC group in terms of % of subjects with rSBA-MenC titre ≥1:8 and anti-PRP concentration ≥0.15 µg/mL, one month after the administration of the vaccine dose

	Menitorix v/s Hib+MenC

Criteria	HibMenC		Hib+ MenC			95% CI	
rSBA-MenC antibodies	N	%	N	%	Difference	LL	UL
≥1:8	281	99.6	98	100	-0.36	-1.99*	3.43
Anti-PRP antibodies							
≥0.15 µg/mL	292	100	100	100	0.00	-1.30*	3.71

HibMenC= *Menitorix* + *Priorix*
Hib+ MenC= *Hiberix* + *MenC-CRM* + *Priorix*
N = number of subjects with available results
% = percentage of subjects with concentration or titres ≥ the specified cut-off
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
*Non-inferiority criterion for the primary endpoint met (the lower limit of the 95% CI >-10 % for vaccine group differences [Menitorix minus Hib plus MenC]).

The antibody responses one month after the administration of a single dose of MENITORIX co-administered with measles-mumps-rubella vaccine, Priorix® is provided in Table 4.

Table 4: Response to a single dose of Menitorix co-administered with Priorix in toddlers primed with Hib during infancy, but not with MenC conjugate

Antigen	Response	DTPa/Hib primed	Hib-OMP primed
Anti-PRP (N=292)	% ≥0.15 µg/ml (n/N)	100% (206/206)	100% (86/86)
	% ≥1 µg/ml (n/N)	97.1% (200/206)	100% (86/86)
	GMC (µg/ml) (N)	28.652 (206)	149.969 (86)
SBA-MenC (N=281)	% ≥1:8 (n/N)	99.5% (197/198)	100% (83/83)
	% ≥1:32 (n/N)	98.5% (195/198)	98.8% (82/83)
	% ≥1:128 (n/N)	84.8% (168/198)	95.2% (79/83)
	GMT (N)	436.0 (198)	615.9 (83)

N= number of subjects with available results
n/%=number/percentage of subjects with titre within pre-specified range
PRP= polyribosylribitol phosphate
SBA-MenC= functional anti-meningococcal serogroup C activity
GMC or GMT= geometric mean antibody concentration or titre

The antibody responses at months 12, 24 and 36 persistence time-points are provided in Table 5.

Table 5: Response to a single dose of Menitorix co-administered with Priorix in toddlers primed with Hib during infancy, but not with MenC conjugate: Antibody levels at Months 12, 24 and 36 persistence time-points (MenC-TT-016 - Hib-MenC-TT-019, ATP cohort for persistence)

Antigen	Response	Time-point		
		Month 12	Month 24	Month 36
Anti-PRP	% ≥0.15 µg/ml (n/N)	99.1 (210/212)	99.1 (212/214)	99.1 (231/233)
	% ≥1 µg/ml (n/N)	82.1 (174/212)	74.8 (160/214)	70.4 (164/233)
	GMC (µg/ml) (N)	3.59 (212)	2.59 (214)	2.23 (233)
SBA-MenC	% ≥1:8 (n/N)	86.7 (183/211)	69.8 (148/212)	64.2 (145/226)
	% ≥1:128 (n/N)	45.5 (96/211)	32.1 (68/212)	25.7 (58/226)
	GMT	87.6 (211)	38.6 (212)	29.8 (226)

N = number of subjects with available results
n/% = number/percentage of subjects with titre within pre-specified range
PRP = polyribosylribitol phosphate
SBA-MenC = functional anti-meningococcal serogroup C activity
GMC or GMT = geometric mean antibody concentration or titre

Long term persistence

Long term antibody persistence was evaluated in subjects primed and boosted with MENITORIX.

A study was conducted in subject primed at 2-3-4 months of age with either MENITORIX co-administered with Infanrix-IPV or with MenC-CRM vaccine co-administered with DTPa-HBV-IPV vaccine. These subjects received a booster dose of MENITORIX co-administered with Priorix at 12-15 months of age. Twelve months after booster vaccination, all subjects (N=261) had anti-PRP antibody concentrations ≥ 0.15 µg/ml, while 89.0% (178/200) of the subjects primed with MENITORIX and 69.5% (41/59) of the subjects primed with a MenC-CRM vaccine had anti-SBA MenC titers ≥ 8.

In an other study 100% of the subjects (n=52) primed with MENITORIX and Infanrix Penta and boosted with MENITORIX at respectively 2-4-6 and 13-14 months of age had anti-PRP concentrations of ≥ 0.15 µg/ml eighteen months after the administration of the MENITORIX booster dose. At that time, 86.5% (45/52) of the subjects had anti-SBA-MenC titres ≥ 1:8.

Estimates of vaccine effectiveness from the UK's routine immunisation programme (using various quantities of three meningococcal serogroup C conjugate vaccines other than MENITORIX) covering the period from introduction at the end of 1999 to March 2004 have demonstrated the need for a booster dose after completion of the primary series (three doses administered at 2, 3 and 4 months). Within one year of completion of the primary series, vaccine effectiveness in the infant cohort was estimated at 93% (95% confidence intervals 67-99%). However, more than one year after completion of the primary series, there was clear evidence of waning protection. Estimates of effectiveness based on a small number of cases to date indicate that there may also be waning protection in children who received a single priming dose as toddlers.

Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

Preclinical safety data

Appropriate safety tests have been performed.

Animal toxicology and/or pharmacology

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and single and repeated dose toxicity studies.

Pharmaceutical Particulars

List of excipients

Powder: Tris, Sucrose
Diluent: Sodium Chloride 0.9% in water for injection.

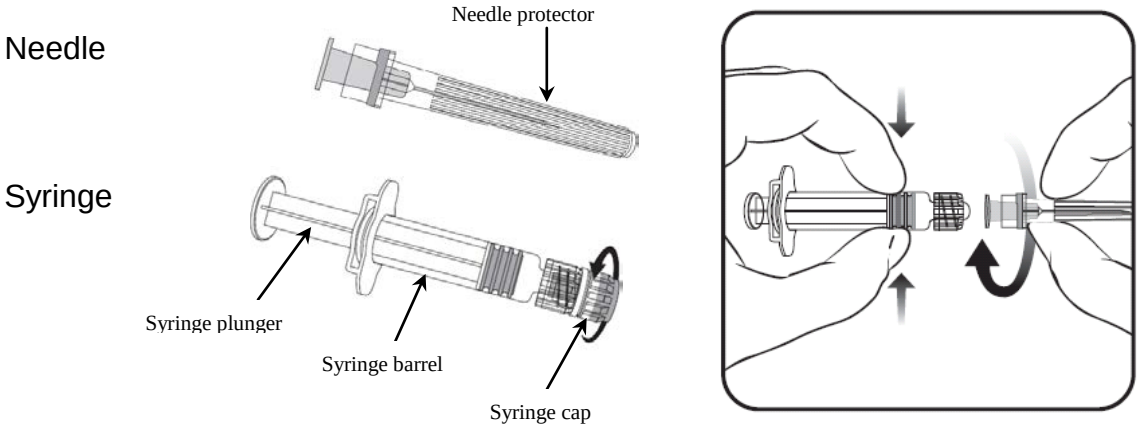
Incompatibilities

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

Instructions for use, handling and disposal

MENITORIX must be reconstituted by adding the entire contents of the pre-filled syringe of diluent to the vial containing the powder.

To attach the needle to the syringe, refer to the below drawing. However, the syringe provided with MENITORIX might be slightly different than the syringe described in the drawing.



1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.

Add the diluent to the powder. After the addition of the diluent to the powder, the mixture should be well shaken until the powder is completely dissolved in the diluent.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

A new needle should be used to administer the vaccine.

Inject the entire contents of the vial.

After reconstitution, the vaccine should be administered promptly or kept in the refrigerator (2°C – 8°C). If it is not used within 24 hours, it should be discarded.

Experimental data show that the reconstituted vaccine could also be kept to 24 hours at ambient temperature (25°C). However, these data are not recommendations for storage.

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

Special precautions for storage

MENITORIX should be stored in a refrigerator between +2°C and +8°C (Do not freeze).

Store in the original packaging in order to protect from light.

During transport, recommended conditions of storage should be respected, particularly in hot climates.

Shelf life

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of MENITORIX is three years from the date of manufacture when the vaccine is stored according to recommendations (see Special precautions for storage).

Nature and contents of the container

MENITORIX is presented as a white powder in a glass vial. The sterile diluent (0.5ml) is clear and colourless and presented in a glass pre-filled syringe.

Vials/pre-filled syringes are made of neutral glass type 1, which conforms to European Pharmacopoeia Requirements.

Medicine Classification

Prescription Medicine

Package Quantities

MENITORIX vaccine: monodose glass vials in packs of 1 or 10.
Diluent: glass pre-filled syringes, 0.5ml in packs of 1 or 10.

Not all pack sizes may be distributed in New Zealand

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Date of Preparation

TBD

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