AUSTRALIAN PRODUCT INFORMATION – VIVAXIM (*SALMONELLA TYPHI* VI POLYSACCHARIDE & HEPATITIS A VIRUS ANTIGEN) VACCINE

1 NAME OF THE MEDICINE

Salmonella typhi Vi polysaccharide and hepatitis A virus antigen.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vivaxim contains a sterile suspension of purified *Salmonella typhi* Vi polysaccharide and formaldehyde-inactivated hepatitis A virus (HAV) antigen (GBM strain) adsorbed onto aluminium hydroxide. Vivaxim is presented in a dual-chamber by-pass syringe. The contents of both chambers are mixed immediately prior to injection by slowly pressing the plunger.

Each 1.0 mL dose of mixed vaccine contains:

Active Ingredients:

Salmonella typhi Vi polysaccharide (Ty 2 strain)	25 micrograms
Hepatitis A virus antigen*	160 antigen units**

* GBM strain cultured on MRC-5 human diploid cells. MRC-5 is a cell line that was derived from human embryonic lung tissue in the 1960s.

** In the absence of an international standardised reference, the antigen content is expressed using an in-house reference.

Excipients with known effects: phenylalanine and residual neomycin.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

The typhoid polysaccharide component is a clear and colourless solution, the hepatitis A component (inactivated, adsorbed) is a cloudy whitish suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Vivaxim is indicated for simultaneous active immunisation against typhoid fever and hepatitis A virus infections in subjects aged 16 and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage is 1 mL of the mixed vaccine.

Vivaxim should be administered by slow intramuscular injection in the deltoid region. Vivaxim must not be administered intradermally or intravenously.

Primary immunisation is achieved with a single dose of Vivaxim.

The vaccine should be administered at least 14 days prior to risk of exposure to both typhoid fever and hepatitis A.

A single dose of Vivaxim does not ensure long-term protection against infection with hepatitis A virus. For long-term protection a booster injection of inactivated hepatitis A vaccine is required 6 to 36 months after the first dose. It has been demonstrated that HAV antibodies persist for many years (at least 10 years) after the booster.

In individuals who remain at risk of typhoid fever, revaccination against typhoid fever should be carried out with a single dose of purified Vi polysaccharide typhoid vaccine with an interval of not more than 3 years, unless it is also appropriate to administer a booster dose of Hepatitis A vaccine at the same time, in which case Vivaxim may be used.

The HA component of Vivaxim produces an adequate booster response when Vivaxim is given 6-36 months after primary vaccination with either inactivated hepatitis A vaccine or 36 months after primary vaccination with Vivaxim.

All parenteral drugs and vaccine products should be inspected visually prior to administration for discolouration or particulate matter. In the event of either being observed, discard the vaccine.

The two vaccine components must only be mixed immediately prior to injection. The contents of the two compartments are mixed by slowly advancing the plunger. The final volume injected is 1 mL.

Shake before injection to obtain a homogeneous suspension. The mixed vaccine is a whitish opalescent suspension.

Contains no antimicrobial agent. Product is for single use only and must not be used in more than one individual. Discard any remaining unused contents

4.3 CONTRAINDICATIONS

Vivaxim should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine or after previous administration of the vaccine or to a vaccine containing the same components or constituents.

Vaccination must be postponed in case of febrile or acute disease.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Do not administer Vivaxim by intravascular injection. Make sure that the needle does not penetrate a blood vessel.

Subcutaneous administration of Vivaxim may increase the risk of local adverse reaction.

Vivaxim should be administered at least 14 days prior to risk of exposure with *S. typhi* and hepatitis A virus.

Prior to Vaccination

Anaphylaxis

As with all injectable vaccines, appropriate medical treatment, such as epinephrine (adrenaline), and supervision should always be readily available in case of a rare anaphylactic reaction following administration of the vaccine (See Section 4.8 Adverse effects (Undesirable effects)).

Hypersensitivity

This vaccine contains formaldehyde as an excipient and it is possible that an allergic reaction may occur. As Vivaxim may contain residual traces of neomycin, caution should be exercised when the vaccine is administered to individuals with hypersensitivity to neomycin (and other antibiotics of the same class). This vaccine contains polysorbate, which may cause local skin reactions.

Syncope

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling injury and manage syncopal reactions.

Special Patient Groups

Thrombocytopenia or Bleeding Disorders

As with all injectable vaccines, the vaccine must be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these individuals.

Immunosuppression

Immunogenicity of Vivaxim could be impaired by immunosuppressive treatment or in immunodeficient individuals. It is recommended to delay vaccination until the completion of any immunosuppressive treatment. Individuals with chronic immunodeficiency such as HIV infection may be vaccinated if the underlying pathology allows the induction of an antibody response, even if limited.

Protection

Because of the long incubation period of hepatitis A, infection may be present but not clinically apparent at the time of vaccination. It is not known whether Vivaxim will prevent hepatitis A in such cases.

A single dose of Vivaxim does not ensure long-term protection against infection with hepatitis A virus. For long term protection a booster dose of inactivated hepatitis A virus vaccine is required 6 to 36 months after vaccination with Vivaxim.

Vivaxim provides protection against the risk of infection related to *S. typhi*, but gives no protection against *Salmonella paratyph*i A or B or against non-typhoidal *Salmonellae*.

Vivaxim does not protect against infection caused by other known liver pathogens including hepatitis B, hepatitis C and hepatitis E viruses.

As with other vaccines, vaccination with Vivaxim may not be expected to protect 100% of susceptible individuals.

Use in the elderly

Immunogenicity and clinical experience with Vivaxim in the elderly is limited.

Paediatric use

No data on the use of Vivaxim in children and adolescents aged below 16 years are available.

Effects on laboratory tests

Interference of Vivaxim with laboratory tests has not been studied.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Vivaxim is a combination of purified Vi polysaccharide typhoid vaccine and inactivated hepatitis A vaccine. Therefore, concomitant administration with other inactivated vaccines using different syringes and at different injection sites may be performed and is unlikely to interfere with the immune response.

Based on data obtained from the concomitant administration of the monovalent vaccines (purified Vi polysaccharide typhoid vaccine and inactivated hepatitis A vaccine) with yellow fever vaccine, no interference with the immune response is expected when Vivaxim is administered concomitantly at a different site with yellow fever vaccine. However, no specific study has been carried out with Vivaxim.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility data available.

Use in pregnancy - Category B2

Animal reproductive studies have not been conducted with Vivaxim.

Data on the use of this vaccine in pregnant women are limited. Therefore, the administration of the vaccine during pregnancy is not recommended.

Vivaxim should be given to pregnant women only if clearly needed, and following an assessment of the risks and benefits.

Use in lactation

It is not known whether this vaccine is excreted in human milk. Caution must be exercised when Vivaxim is administered to a nursing mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Within each system organ class the adverse events are ranked under headings of frequency, most frequent reactions first, using the following convention:

Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10 000, <1/1000), Very rare (<1/10 000), Not known (cannot be estimated from the available data).

Data from clinical studies

The safety profile of Vivaxim was evaluated in nearly 1300 subjects during controlled clinical studies. The most commonly reported reactions were those occurring at the injection site.

Pain at the injection site was reported by 89.9% of subjects following administration of Vivaxim compared with 83.2% of subjects who received monovalent Vi polysaccharide typhoid vaccine and inactivated hepatitis A vaccine concomitantly at separate injection sites.

Local reactogenicity: the following data show the risk of severe local reactions (or > 5cm) or reactions lasting more than 72 hours (Table 1).

Table 1 - Local reactions (severe or >72 hours) in the 7 days following vaccination

	HA/Vi N=787 n (subjects)	%
AT LEAST ONE LOCAL EVENT	**719**	**91.4**
Pain	**710**	**90.2**
Severe Pain	34	4.3
Pain > 72 h	167	21.2
Erythema	**124**	**15.8**
Erythema > 5 cm	8	1.0
Erythema > 72 h	23	2.9
Induration/Oedema	**254**	**32.3**
Induration/Oedema > 5 cm	52	6.6
Induration/Oedema > 72 h	53	6.7
Ecchymosis	**26**	**3.3**
Ecchymosis. > 5 cm	1	0.1
Ecchymosis > 72 h	11	1.4

The adverse reactions observed with Vivaxim were as follows:

Nervous system disorders

Very common: headache

Uncommon: dizziness

Gastrointestinal disorders

Common: nausea, diarrhoea

Skin and subcutaneous tissue disorders

Uncommon: pruritus; rash

Musculoskeletal and connective tissue disorders

Very *common*: myalgia

Common: arthralgia.

General disorders and administration site conditions

Very common:	injection site pain, injection site induration, injection site oedema, injection site erythema, asthenia.
Common:	malaise, pyrexia.

Data from post-marketing experience

Based on spontaneous reporting, the following additional adverse events have been reported during the commercial use of Vivaxim. These events have been very rarely reported; however, as exact incidence rates cannot be calculated precisely, their frequency is qualified as "Not known".

Immune system disorders

- anaphylactic/anaphylactoid reactions, including shock; serum sickness.

Nervous system disorders

- vasovagal syncope

Gastrointestinal disorders

- vomiting, abdominal pain.

Skin and subcutaneous tissue disorders

- urticaria.

Investigations

- transaminases increased (mild and reversible).

Additional adverse events were not reported with Vivaxim but were reported respectively following use of the monovalent Typhoid polysaccharide vaccine or the monovalent inactivated hepatitis A vaccine.

Respiratory, thoracic and mediastinal disorders

- Not known: asthma

General disorders and administration site condition

- Very rare: injection site nodule

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at

www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 OVERDOSE

Cases of administration of more than the recommended dose (overdose) have been reported with Vivaxim. When adverse reactions were reported, the information was consistent with the known safety profile of Vivaxim described in Section 4.8 Adverse effects (undesirable effects).

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: J: ANTIINFECTIVES FOR SYSTEMIC USE; J07 (vaccines) CA (Bacterial and viral vaccines, combined) 10 (typhoid-hepatitis A)

Mechanism of action

A minimum of fourteen days after vaccination is necessary to allow development of an adequate immune response prior to a potential exposure.

Typhoid fever seroprotection threshold is not known and estimates vary between 0.6µg/mL and 1.5µg/mL. Seroprotection level of ≥ 1µg/mL has been used in the studies supporting immunogenicity of Vivaxim. There is a consensus on the 4-fold increase as a criterion for seroconversion and this is used in all clinical trials.

By consensus hepatitis A seroprotection level is ≥ 20 mIU/mL.

The efficacy of the combined vaccine has not been demonstrated in field studies

Clinical trials

Immunogenicity

The combined vaccine, Vivaxim, produced immune responses for primary vaccination and for booster vaccination that were non-inferior to those of the two monovalent vaccines Typhim Vi and Avaxim.

Study 1:

The immunogenicity and safety of Vivaxim have been determined by this pivotal study designed to compare the immunogenicity of *S. typhi* Vi and hepatitis A antigens administered either together, using a dual chamber syringe (Vivaxim), or separately at two different sites

(Typhim Vi and Avaxim vaccines). The study was open label and randomised and included 360 adult subjects; 179 in the Vivaxim group and 181 in the Typhim Vi + Avaxim group.

Forty subjects, 17 in the Vivaxim group and 32 in the separately administered vaccine group were found to be seropositive at inclusion and were excluded from the analysis of immunogenicity. Consequently the per-protocol population evaluated 28 days after vaccination consisted of:

Vivaxim – 172 subjects in the typhoid Vi analysis, and 157 for the hepatitis A analysis.

Typhim Vi and Avaxim – 173 in the typhoid Vi analysis, and 149 in the hepatitis A analysis.

Twenty eight days after the Vivaxim injection, the anti-typhoid Vi seroconversion rate (≥ four-fold rise in titre) was 84.7% and the anti-hepatitis A seroprotection rate (≥ 20 mIU/mL) was 98.7% (Table 2 and Table 3).

Study 1 Follow-Up:

A follow-up study examined residual antibody levels 3 years after the primary vaccination. At this time, a subset of the original subjects underwent re-vaccination with the combined vaccine: antibody response was recorded 28 days later.

Three years after primary vaccination with Vivaxim, the typhoid Vi seroprotection rate (percent ≥ 1µg/mL) was 32.1%. One month following re-vaccination with Vivaxim the seroprotection rate for typhoid Vi increased to 69.6%; the seroconversion rate for typhoid Vi was 26.1%.

Three years after primary vaccination with Vivaxim the hepatitis A seroprotection rate (percent ≥ 20 mIU/mL) was 99.1%. The seroprotection rate for hepatitis A increased to 100% 28 days after re-vaccination.

Results of the follow-up study are shown in Table 4 and Table 5.

Study 2:

The batch consistency of Vivaxim was demonstrated in a multicentric double-blind randomised study of adult subjects, using 3 batches of the combined vaccine. The seroconversion rate for typhoid antibody was 92.1% and for hepatitis A antibody was 100% (Tables 1 and 2).

Combined Studies 1 and 2:

The two studies combined included a total of 789 subjects. The combined seroconversion rate for anti-Vi antibody was 90.3% and seroprotection rate for anti-HAV antibody was 99.7% (Table 2 and Table 3).

Study 3:

A single centre, open, randomised study of adult subjects, demonstrated non-inferiority of the hepatitis booster response of the combined vaccine Vivaxim compared with the single component inactivated hepatitis A vaccine, Avaxim. The primary vaccination of all subjects

was Avaxim. Six months after initial vaccination subjects underwent booster vaccination and antibody levels were measured 28 days later (Table 6).

Table 2 - Combined studies 1 and 2 Anti-typhoid Vi antibody response after vaccination with Vivaxim

	14 days after vaccination			
Study	**Number of subjects**	**Seroconversion[1] (%) [95%CI[2]]**	**Seroprotection[3] (%) [95%CI]**	**GMT [95% CI]**
1	177	86.4% [80.5 - 91.1]	89.3% [83.7- 93.4]	2.98 [2.61-3.39]
2	-	-	-	-
All	177	86.4% [80.5 - 91.1]	89.3% [83.7 - 93.4]	2.98 [2.61 - 3.40]
	28 days after vaccination			
Study	**Number of subjects**	**Seroconversion (%) [95% CI]**	**Seroprotection (%) [95% CI]**	**GMT [95% CI]**
1	176	84.7% [78.5 - 89.6]	85.2% [79.1 - 90.1]	2.64 [2.31 - 3.02]
2	609	92.1% [89.7 - 94.1]	90.6% [88.0 - 92.8]	2.89 [2.71 - 3.09]
All	785	90.3% [88.0 - 92.3]	89.4% [87.1 - 91.5]	2.83 [2.67 - 3.01]

1. Seroconversion – four fold rise in antibody titres
2. CI – confidence interval
3. Seroprotection – ≥ 1 μg/mL

Table 3 - Combined studies 1 and 2 Hepatitis A antibody response after vaccination with Vivaxim [1]

	14 days after vaccination			**28 days after vaccination**		
Study	**Number of subjects**	**Seroprotection[2] (%) [95%CI3]**	**GMT [95%CI]**	**Number of subjects**	**Seroprotection (%)[95% CI]**	**GMT [95% CI]**
1	160	95.6% [91.2 – 98.2]	235 [191 – 290]	159	98.7% [95.5 – 99.8]	783 [654 – 938]
2	-	-	-	581	100% [99.4 – 100]	882 [817 – 951]
All	160	95.6% [91.2 – 98.2]	235 [191 – 290]	740	99.7% [99.0 – 100]	858 [799 – 921]

1. In previously seronegative subjects
2. Seroprotection – ≥ 20mIU/mL
3. CI – confidence interval

Table 4 - Study 1 – Follow-up Typhoid antibody persistence and response to re-vaccination with Vivaxim

	Year 1	Year 2	Year 3	Year 3 +28 days[1]
Number of subjects	139	124	112	46
GMT[2]	0.850	0.698	0.641	1.52
95% CI	0.716 – 1.01	0.585 – 0.834	0.530 – 0.776	1.12 – 2.06
Percent seroprotected[3]	44.6	40.3	32.1	69.6
95% CI	36.2 – 53.3	31.6 – 49.5	23.6 – 41.6	54.2 – 82.3

1. 28 days after re-vaccination
2. GMT – Geometric Mean Titre
3. greater than or equal to 1 μg/mL

Table 5 - Study 1 – Follow-up Hepatitis A antibody persistence and response to re-vaccination with Vivaxim

	Year 1	Year 2	Year 3	Year 3 +28 days1
Number of subjects	140	124	112	46
GMT2	548	419	425	15,063
95% CI	443 - 678	340 - 518	345 - 524	11,742 – 19,323
Percent seroprotected3	99.3	98.4	99.1	100
95% CI	96.1 - 100	94.3 – 99.8	95.1 - 100	92.3 - 100

1. 28 days after re-vaccination
2. GMT – Geometric Mean Titre
3. greater than or equal to 20 mIU/mL

Table 6 - Study 3 Hepatitis A antibody responses to primary and booster vaccination

	Combined typhoid and hepatitis A vaccine Vivaxim			Inactivated hepatitis A vaccine Avaxim		
	Day 0	6 months	7 months	Day 0	6 months	7 months
Subject numbers	53	53	53	55	55	55
GMT[1]	10.5	219	4,576	10.7	194	3,760
Seroprotection rate (≥20mIU/mL)	0	100	100	0	100	100
95%CI	0–6.7	93.3–100	93.3-100	0-6.5	93.5-100	93.5-100

1. GMT – Geometric Mean Titre

5.2 PHARMACOKINETIC PROPERTIES

No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Vivaxim has not been evaluated for genotoxicity.

Carcinogenicity

Vivaxim has not been evaluated for carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 1.0 mL dose of mixed vaccine contains:

Other components:

Salmonella typhi Vi polysaccharide typhoid vaccine components:

Phosphate buffer solution containing:

Sodium chloride	4.150 mg
Dibasic sodium phosphate dihydrate	0.065 mg
Monobasic sodium phosphate dihydrate	0.023 mg
Water for injections	up to 0.5 mL

Inactivated hepatitis A virus vaccine component:

Aluminum hydroxide hydrate(quantity expressed as aluminium)	0.3 mg
Phenoxyethanol (preservative)	2.5 microlitres
Formaldehyde (preservative)	12.5 micrograms
Medium 199 (Hanks)*	up to 0.5 mL

* Supplemented with polysorbate 80. Medium 199 (Hanks) without phenol red, is a complex mixture of amino acids including phenylalanine, mineral salts, vitamins and other components such as glucose, diluted in water for injections and with a pH adjusted with hydrochloric acid or sodium hydroxide.

Neomycin (≤5 µg/ml) and bovine serum albumin (< 10 nanograms) may be present as residual traces.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

6.2 INCOMPATIBILITIES

This vaccine must not be mixed with other vaccines or medicinal products.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store between 2°C and 8°C (Refrigerate. Do not freeze). Product that has been exposed to freezing should not be used. Do not use after expiration date. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Vivaxim is contained in a type I glass, dual chamber, by-pass syringe (1 mL) with an elastomer (chlorobromobutyl) plunger stopper, elastomer (chlorobromobutyl) tip cap and elastomer (chlorobromobutyl) by-pass stopper.

The purified Vi polysaccharide typhoid vaccine (solution for injection) is contained in the chamber of the syringe closest to the needle, and the inactivated hepatitis A vaccine (suspension for injection) in the chamber closest to the plunger-stopper.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Not relevant to vaccines.

CAS number

Not relevant to vaccines.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Australia:
sanofi-aventis australia pty ltd
Talavera Corporate Centre – Building D
12 – 24 Talavera Road
Macquarie Park NSW 2113
Australia
Tel: 1800 818 806

New Zealand:
sanofi-aventis new zealand limited
Level 8, 56 Cawley St

Ellerslie
Auckland
New Zealand
Tel: 0800 283 684

9 DATE OF FIRST APPROVAL

24 September 2002

10 DATE OF REVISION

05 March 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted in line with the new form
All	Tradenames updated
2;4; 5; 6	Editorial
6.2	Incompatibility information added
6.3	Shelf life added
8	Phone numbers updated