

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

ViVAXIM®

**Combined Purified Vi Polysaccharide Typhoid and
Inactivated Hepatitis A Vaccine**

Suspension for injection (25µg purified *Salmonella typhi* Vi capsular polysaccharide + 160U
inactivated Hepatitis A virus / 1.0 mL)

(For active immunization against Typhoid Fever and Hepatitis A Infection)

ATC Code: J07CA10

Manufactured by:
Sanofi Pasteur SA
Lyon, France

Date of Revision:
September 2015

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

Date of Approval:
2015-10-01
Control # 187411

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION.....	3
DESCRIPTION.....	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS	5
WARNINGS AND PRECAUTIONS	5
ADVERSE REACTIONS.....	7
DRUG INTERACTIONS.....	9
DOSAGE AND ADMINISTRATION.....	10
OVERDOSAGE	11
ACTION AND CLINICAL PHARMACOLOGY	12
STORAGE AND STABILITY.....	12
DOSAGE FORMS, COMPOSITION AND PACKAGING	12
PART II: SCIENTIFIC INFORMATION	15
PHARMACEUTICAL INFORMATION.....	15
CLINICAL TRIALS.....	15
REFERENCES.....	20
PART III: PATIENT MEDICATION INFORMATION	22

<

ViVAXIM®

Combined Purified Vi Polysaccharide Typhoid and Inactivated Hepatitis A Vaccine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration

Intramuscular injection.

Dosage Form/Strength

Suspension for injection.

Each 1 mL dose is formulated to contain:

Active Ingredients

Salmonella typhi (Ty2 strain) purified Vi capsular polysaccharide – 25 µg
Inactivated hepatitis A virus (HAV) (GBM strain) – 160 antigen units (U)

Clinically Relevant Non-medicinal Ingredients

Excipients: sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, aluminum hydroxide (expressed as aluminum), 2-phenoxyethanol, formaldehyde, polysorbate 80, Medium 199 Hanks.

Manufacturing process residuals: neomycin.

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.

DESCRIPTION

ViVAXIM® [Combined Purified Vi Polysaccharide Typhoid and Inactivated Hepatitis A Vaccine] is a combination vaccine consisting of purified Vi Polysaccharide Typhoid and Inactivated Hepatitis A supplied in a dual chamber syringe. The vaccine is mixed immediately before administration resulting in a cloudy whitish suspension.

This vaccine is a buffered solution (without phenol) of purified *Salmonella typhi* Vi capsular polysaccharide (Ty2 strain) and a suspension of purified and formaldehyde-inactivated HAV, obtained from GBM strain, cultured on MRC-5 human diploid cells. HAV is adsorbed onto aluminum.

INDICATIONS AND CLINICAL USE

ViVAXIM® is indicated for simultaneous active immunization against infection caused by *S. typhi*, the organism that causes typhoid fever, and HAV in persons 16 years of age or older. ViVAXIM® can be used for hepatitis A primary immunization or booster and for typhoid primary

immunization or revaccination. (See DOSAGE AND ADMINISTRATION)

There is no contraindication to administering ViVAXIM® to someone who is already immune to hepatitis A. (1)

HAV vaccination is recommended in the following situations: (2)

- 1) Pre-exposure immunization of persons at increased risk of infection or severe hepatitis A (HA).
 - Travellers to HA endemic areas (including military personnel and humanitarian relief workers) or immigrants from HA endemic areas.
 - Household or close contacts of children adopted from HA endemic countries
 - Populations or communities at risk of HA outbreaks or in which HA is highly endemic
 - Persons with lifestyle risks for infection, including those who use illicit drugs and men who have sex with men (MSM).
 - Persons who have chronic liver disease from any cause, as they may be at risk of more severe disease if infection occurs.
 - People with hemophilia A or B receiving plasma-derived products.
 - Persons who handle non-human primates and workers involved in research who may be exposed to HA virus
- 2) Post-exposure immunization for household and close contacts of proven or suspected cases of hepatitis A.

Typhoid vaccination is recommended in the following situations: (3)

- 1) Travellers to endemic or epidemic areas or where sanitary conditions may be doubtful and where travellers may be exposed to potentially contaminated food and water, particularly when prolonged exposure is anticipated.
- 2) Travellers with reduced or absent gastric acid secretion.
- 3) People with ongoing household or intimate exposure to an *S. typhi* carrier.
- 4) Laboratory workers who frequently handle cultures of *S. typhi*.

The complete, current recommendations by NACI can be accessed at www.phac-aspc.gc.ca/publicat/cig-gci/

Pediatrics

ViVAXIM® is not indicated for immunization of persons below the age of 16 years.

Geriatrics

ViVAXIM® is indicated for immunization of persons 16 years of age or older.

CONTRAINDICATIONS

Hypersensitivity

Known systemic hypersensitivity reaction to any component of ViVAXIM® 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. (4) (See SUMMARY PRODUCT INFORMATION.)

WARNINGS AND PRECAUTIONS

General

Before administration of ViVAXIM®, health-care providers should inform the recipient or the parent or guardian of the recipient of the benefits and risks of immunization, inquire about the recent health status of the recipient, review the recipient'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 with respect to information to be provided to the recipient, parent or guardian before immunization.

Because of the incubation period of hepatitis A disease, infection may be present but not clinically apparent at the time of vaccination. It is not known whether ViVAXIM® will prevent hepatitis A in this case.

As with any vaccine, ViVAXIM® may not protect 100% of vaccinated individuals. Travellers should take all necessary precautions to avoid contaminated food and water. This is of particular concern when the vaccine is administered less than 2 weeks before departure, as optimum antibody protection may not yet be achieved.

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

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.

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

Do not administer intradermally.

ViVAXIM® should not be administered into the buttocks.

Febrile or Acute Disease: Vaccination should be postponed in cases of an acute or febrile disease. (5) However, a disease with a low-grade fever should not usually be a reason to postpone vaccination.

Protection

ViVAXIM® does not provide protection against species of *Salmonella* other than *Salmonella typhi* or against other bacteria that cause enteric disease; it does not provide protection against

infection caused by hepatitis B virus, hepatitis C virus, delta virus, hepatitis E virus or by other liver pathogens, other than HAV.

Hematologic

Because any intramuscular injection can cause an injection site hematoma in persons with any bleeding disorders, such as hemophilia or thrombocytopenia, or in persons on anticoagulant therapy, intramuscular injections with ViVAXIM® 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.

In exceptional circumstances (e.g., in patients with thrombocytopenia or in patients at risk of hemorrhage) the vaccine may be administered by the subcutaneous route, however, this may be associated with a higher risk of local reaction including injection site nodule. (4)

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 ViVAXIM® even in persons with no prior history of hypersensitivity to the product components. (See DOSAGE FORMS, COMPOSITION AND PACKAGING.)

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. (4) Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management. (4) For instructions on recognition and treatment of anaphylactic reactions, see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment. (4) Nevertheless, vaccination of persons with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited. (4) (5)

Pregnant Women

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.

Nursing Women

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

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.

In controlled clinical studies using ViVAXIM® the most commonly reported reactions were those occurring at the injection site.

In a clinical trial comparing ViVAXIM® with the two monovalent vaccines given simultaneously at separate sites, pain at the injection site was reported by 89.9% of subjects (4.5% severe) following administration of ViVAXIM® compared with 84.9% of subjects (5% severe) who received monovalent Vi polysaccharide typhoid vaccine and inactivated hepatitis A vaccine at separate injection sites. (6) (7) (8)

Table 1: Frequency (%) of Reactions Observed within 7 Days Following a Dose of ViVAXIM®

Reactions	% of Vaccinees with a Reaction (N = 178)
Nervous System Disorders	
Headache	15.2
Dizziness	1.1
Gastrointestinal Disorders	
Nausea	2.8
Diarrhea	2.8
Skin and Subcutaneous Tissue Disorders	
Pruritus	0.6
Rash	0.6
Musculoskeletal, Connective Tissue and Bone Disorders	
Myalgia	16.3
Arthralgia	0.6
General Disorders and Administration Site Conditions	
Pain at the injection site	89.9
Induration/Oedema at the injection site	28.1
Asthenia	16.9
Erythema at the injection site	10.1
Fever	4.5
Malaise	3.4

Post-Market Adverse Reactions

The following additional adverse events have been spontaneously reported during the post-marketing use of ViVAXIM®. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Decisions to include these events in labelling were based on one or more of the following factors: 1) severity of the event, 2) frequency of reporting, or 3) strength of causal connection to ViVAXIM®.

Immune System Disorders

anaphylactic/anaphylactoid reaction, including shock, serum sickness

Nervous System Disorders

vasovagal syncope

Gastrointestinal Disorders

vomiting, abdominal pain

Skin and Subcutaneous Tissue Disorders

urticaria

Investigation

transaminases increased (mild and reversible)

The following additional adverse reactions were not reported with ViVAXIM® but were reported respectively in association with TYPHIM Vi® [*Salmonella typhi* Vi capsular polysaccharide vaccine] or AVAXIM® [Hepatitis A Vaccine Inactivated]:

Respiratory, Thoracic and Mediastinal Disorders

asthma

General Disorders and Administration Site Condition

injection site nodule

Physicians, nurses and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and to the Global Pharmacovigilance Department, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

DRUG INTERACTIONS

Vaccine-Drug Interactions

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

Concomitant Vaccine Administration

ViVAXIM® may be administered simultaneously with immune globulin at separate sites with separate syringes. (4) Hepatitis A seroconversion rates are not modified, but hepatitis A antibody titres could be lower than after vaccination using the vaccine alone. (9)

As the vaccine is inactivated, concomitant administration of other vaccine(s) given at other injection sites is unlikely to interfere with immune responses.

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 of any of these antigens would be expected when ViVAXIM® is administered concurrently at a different site with yellow fever vaccine. (10) No interaction with other medication is currently known.

Vaccines administered simultaneously must be given using separate syringes at separate sites.

ViVAXIM® should not be mixed in the same syringe with other parenterals.

DOSAGE AND ADMINISTRATION

Recommended Dose

ViVAXIM® should be administered as a single injection of 1 dose (1 mL) by the intramuscular route.

To provide long-term protection against infection caused by HAV, a booster injection of inactivated hepatitis A vaccine (such as AVAXIM®) should be given 6 to 36 months later. Alternatively, ViVAXIM® can be given as a booster vaccine at 36 months in those persons who require protection against typhoid fever.

ViVAXIM® may be used as a booster vaccine in persons who received ViVAXIM® 36 months earlier and who require a hepatitis A booster and protection against typhoid fever.

Administration

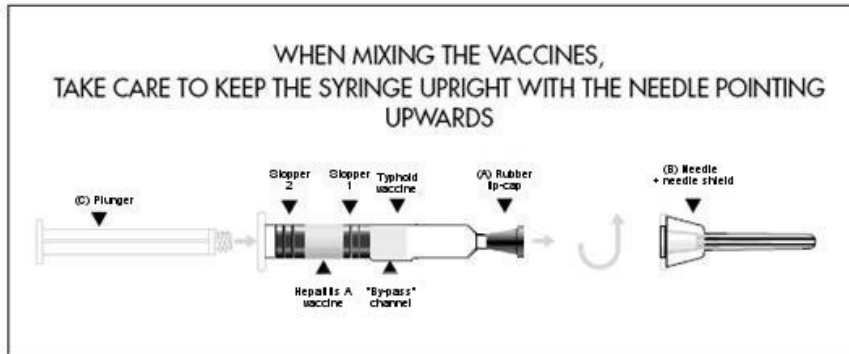
Inspect for extraneous particulate matter and/or discolouration before use. (See DESCRIPTION.) If these conditions exist, the product should not be administered.

The purified Vi polysaccharide typhoid vaccine is contained in the chamber of the syringe closest to the syringe tip and the inactivated hepatitis A vaccine in the chamber closest to the plunger.

The two vaccine components should only be mixed **immediately** before injection. The final volume to be injected is 1 mL.

Aseptic technique must be used. Use a separate sterile disposable unit for each individual patient to prevent disease transmission. Needles should not be recapped and should be disposed of according to biohazard waste guidelines.

Figure 1. Instructions for Use – Dual Chamber Syringe



1. Remove the tip-cap (A).
2. Attach needle and needle shield (B) to the syringe.
3. Screw the plunger rod (C) into the plunger stopper (stopper 2).
4. Shake the syringe; then mix the vaccine components by slowly pushing the plunger, keeping the needle upwards. The vaccine in the lower chamber moves into the upper chamber by means of the by-pass channel.
5. Shake vigorously until a homogeneous cloudy, whitish suspension is achieved.
6. Holding the needle shield at the tip, remove by pulling upwards without twisting.
7. Proceed immediately with the injection. The stoppers may separate but ensure that stopper 2 does not reach the by-pass channel in order to avoid any leakage of liquid. Administer the vaccine **intramuscularly** (I.M.). The preferred site of injection is the deltoid muscle.

Give the patient a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. This permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

HAV is a single serotype, ribonucleic acid (RNA) virus of the *Picornaviridae* family. HAV is transmitted via the fecal-oral route, which can occur from direct person-to-person contact, from contamination of the environment or objects, or through contaminated food or water. (2)

Salmonella typhi is the etiological agent of typhoid fever, an acute, febrile enteric disease transmitted by contaminated water and food. (3)

Mechanism of Action

TYPHIM Vi® confers significant protection against typhoid fever based on the production of measurable antibodies, predominantly of the IgG class. (11) AVAXIM® confers immunity against HAV infection by inducing the production of specific anti-HAV antibodies.

Pharmacodynamics

In 2 clinical studies involving 787 participants, after the primary vaccination, the seroprotection rate for HAV (% ≥ 20 mIU/mL) was 95.6% after 14 days (n = 153) and 99.7% after 28 days (n = 738). The seroprotection rate for Vi (% ≥ 1 $\mu\text{g/mL}$) was 89.3% after 14 days (n = 158) and 90.3% after 28 days (n = 707). (6)

Duration of Effect

Revaccination against typhoid fever should be carried out with a single dose of purified Vi polysaccharide typhoid vaccine (such as TYPHIM Vi® or ViVAXIM®) at an interval of not more than 3 years in subjects who remain at risk.

Data relative to long-term persistence of anti-HAV antibodies following vaccination with ViVAXIM® are not currently available. Published data suggest that anti-HAV antibodies persist beyond 10 years after the booster vaccination in healthy individuals. (12) (13) (14) (15) (16) According to the National Advisory Committee on Immunization (NACI), kinetic models of antibody decline suggest that protective levels of anti-HAV antibody will likely persist for at least 20 years. (16) (2)

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.

The vaccine must be administered immediately after mixing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

ViVAXIM® is supplied in a dual chamber syringe which contains 0.5 mL of purified Vi polysaccharide typhoid vaccine (clear colourless solution for injection) and 0.5 mL of inactivated hepatitis A vaccine (cloudy whitish suspension for injection) which are mixed immediately before administration resulting in a cloudy whitish suspension.

Composition

The dual chamber syringe contains 0.5 mL of purified Vi polysaccharide typhoid vaccine and 0.5 mL of inactivated hepatitis A vaccine.

Each single dose (1 mL) is formulated to contain:

First Chamber

Active Ingredient

Salmonella typhi (Ty2 strain) purified Vi capsular polysaccharide 25 µg

Other Ingredients

Phosphate buffer solution containing:

Sodium chloride	4.150 mg
Disodium phosphate dihydrate	0.065 mg
Sodium dihydrogen phosphate dihydrate	0.023 mg
Water for injection	qs to 0.5 mL

Second Chamber

Active Ingredient

Inactivated hepatitis A Virus, GBM strain 160 antigen units†

Other Ingredients

2-phenoxyethanol	2.5 µL
Formaldehyde	12.5 µg
Aluminum hydroxide (expressed as aluminum)	0.3 mg
Medium 199 Hanks/water for injection‡	qs to 0.5 mL
Polysorbate 80	≤750 µg

Manufacturing Process Residual: Neomycin is present in trace amounts.

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

‡ Medium 199 Hanks (without phenol red) is a mixture of amino acids, mineral salts, vitamins and other components supplemented with polysorbate 80.

ViVAXIM® is supplied in a pre-filled single dose, dual chamber syringe.

The syringes are made of Type 1 glass. The plunger stoppers and needle shield for the syringe do not contain latex (natural rubber).

ViVAXIM® is supplied in packages of:

1 x 1 mL (single dose) dual chamber syringe without attached needle.

Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business Hours: 7:30 a.m. to 7:30 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of September 2015.

Manufactured by:
Sanofi Pasteur SA
Lyon, France

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R4-0915 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Combined Purified Vi Polysaccharide Typhoid and Inactivated Hepatitis A Vaccine

Product Characteristics

ViVAXIM® is a sterile, cloudy, whitish suspension of inactivated hepatitis A and *Salmonella typhi*.

The Vi antigen contained in TYPHIM Vi® vaccine is extracted from the bacterial capsule of *Salmonella typhi* strain Ty2. Each dose of purified Vi polysaccharide typhoid vaccine contains 25 µg.

AVAXIM®'s active ingredient is a purified and formaldehyde-inactivated HAV obtained from the GBM strain cultured on MRC-5 human diploid cells. Hepatitis A virus is adsorbed onto aluminum. Each dose (0.5 mL) of inactivated hepatitis A vaccine contains 160 antigen units (in the absence of an international standardized reference, the antigen content is expressed using an in-house reference).

CLINICAL TRIALS

Table 2: Summary of Demographics and Study Design of the Trials with ViVAXIM®

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects	Age Range	Gender
AVi01398 (7)	Multicentre, open, randomised comparison study between HA/Vi vaccine and concomitant administration of hepatitis A and typhoid fever vaccines Follow-up at Year 1, 2 and 3. Revaccination with ViVAXIM® at Year 3.	1 Dose, 1.0 mL I.M. of HA/Vi Vaccine or 1 Dose, 0,5 mL I.M. each of Hepatitis A and Typhoid Fever Vaccine	N = 360	16 – 65 Years	Males N = 144 Females N = 216
AVi02398 (8)	Multicentre, double-blind, randomized comparison of three batches of hepatitis A and typhoid fever combined vaccine (HA/Vi)	1 Dose, 1.0 mL I.M. of HA/Vi Vaccine	N = 610	16 – 59 Years	Males N = 276 Females N = 334

Immunogenicity

TYPHIM Vi® confers significant protection against typhoid fever based on the production of measurable antibodies, predominantly of the IgG class. (11)

AVAXIM® confers immunity against HAV infection by inducing the production of specific anti-hepatitis A virus antibodies.

In a clinical trial conducted in adults aged 16 - 65 years, 179 persons received ViVAXIM® and 181 received AVAXIM® in one arm and TYPHIM Vi® in the other arm. Equivalent seroconversion rates were seen, both at 14 and 28 days after vaccine administration. In another clinical trial conducted in adults aged 16 - 59 years, 610 persons received one dose of ViVAXIM®. Antibody responses are in Table 3 and Table 4. (6)

Table 3: Antibody Response to Vi 14 and 28 Days Post-Vaccination with ViVAXIM® (6)

Anti-Vi titre (µg/mL)	Day 0	Day 14	Day 28
		N = 787	N = 177
GMT (95% CI)*	0.206 (0.196 - 0.217)	2.98 (2.61 - 3.40)	2.83 (2.67 - 3.01)
≥1 µg/mL	N = 35	N = 158	N = 702
% (95% CI)	4.4 (3.1 - 6.1)	89.3 (83.7 - 93.4)	89.4 (87.1 - 91.5)
≥4-fold rise	-	N = 153	N = 707
% (95% CI)	-	86.4 (80.5 - 91.1)	90.3 (88.0 - 92.3)

* 95% CI: 95% confidence interval

Table 4: Antibody Response to HAV 14 and 28 Days Post-Vaccination with ViVAXIM® in Initially Anti-HAV Seronegative Subjects

Anti-HAV titre (mIU/mL)	Day 0	Day 14	Day 28
		N = 743	N = 160
GMT (95% CI)*	6.14 (5.93 - 6.35)	232 (188 - 285)	858 (799 - 921)
≥20 mIU/mL	N = 0	N = 153	N = 738
% (95% CI)	0.0 (0.0 - 0.5)	95.6 (91.2 - 98.2)	99.7 (99.0 - 100)

* 95% CI: 95% confidence interval

To assess the persistence of antibody, individuals in the comparative trial were followed for 3 years. During the three-year follow-up period, antibody trends for both valences were similar in both groups as shown in Table 5 and Table 6. The anti-Vi titres and percentage of subjects seroconverted gradually declined over the three years in both groups. Regarding anti-HAV titres, whether the group had initially received ViVAXIM® or AVAXIM® and TYPHIM Vi® more than 99% of subjects were still seroconverted 3 years later. (6)

Table 5: Antibody Response to Vi

	ViVAXIM®			TYPHIM Vi® and AVAXIM®		
	Year 1 N = 139	Year 2 N = 124	Year 3 N = 112	Year 1 N = 140	Year 2 N = 117	Year 3 N = 104
Anti-Vi titre (µg/mL)						
GMT	0.85	0.698	0.641	0.944	0.704	0.662
95% CI	0.716 - 1.01	0.585 - 0.834	0.530 - 0.776	0.769 - 1.16	0.564 - 0.878	0.520 - 0.843
≥1 µg/mL						
%	44.6	40.3	32.1	44.3	41	35.6
95% CI	36.2 - 53.3	31.6 - 49.5	23.6 - 41.6	35.9 - 52.9	32.0 - 50.5	26.4 - 45.6

Table 6: Antibody Response to HAV

	ViVAXIM®			TYPHIM Vi® and AVAXIM®		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Anti-Vi titre (µg/mL)						
GMT	548	419	425	321	257	258
95% CI	443 - 678	340 - 518	345 - 524	265 - 390	204 - 324	202 - 329
≥20 mIU/mL						
%	99.3	98.4	99.1	99.3	98.3	99
95% CI	96.1 - 100	94.3 - 99.8	95.1 - 100	96.1 - 100	93.9 - 99.8	94.7 - 100

Three years after the initial immunization, a sub-group of 102 individuals was re-immunized with ViVAXIM®. Complete serology results were available for 46 individuals who had initially received ViVAXIM® and 37 individuals who had initially received AVAXIM® and TYPHIM Vi® concomitantly at separate sites. Comparison of geometric mean titres (GMTs) 28 days after ViVAXIM® injection at year 3 indicated that, for both valences, the GMTs obtained for the ViVAXIM® group are non-inferior to the GMTs obtained for the group receiving AVAXIM® and TYPHIM Vi®. (6) (7)

Safety

In controlled clinical studies using ViVAXIM® the most commonly reported reactions were those occurring at the injection site.

In a clinical trial comparing ViVAXIM® with the two monovalent vaccines given simultaneously at separate sites, pain at the injection site was reported by 89.9% of subjects (4.5% severe) following administration of ViVAXIM® compared with 84.9% of subjects (5% severe) who received monovalent Vi polysaccharide typhoid vaccine and inactivated hepatitis A vaccine at separate injection sites. (6)

Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business Hours: 7:30 a.m. to 7:30 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of September 2015.

Manufactured by:

Sanofi Pasteur SA

Lyon, France

Distributed by:

Sanofi Pasteur Limited

Toronto, Ontario, Canada

R4-0915 Canada

REFERENCES

- 1 Zuckerman J, et al. Comparison of the safety and immunogenicity of two inactivated hepatitis A vaccines. *Adv Therapy* 1997;14(3):116-24.
- 2 National Advisory Committee on Immunization (NACI). Part 4 - Active Vaccines: Hepatitis A Vaccine. In: *Canadian Immunization Guide*. [Online]. 2012. Available from: URL:<http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-hepa-eng.php>
- 3 National Advisory Committee on Immunization (NACI). *Canadian Immunization Guide, Part 4 - Active Vaccines: Typhoid Vaccine* [Online]. Ottawa: Public Health Agency of Canada; 2014. Available from: <http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-typh-eng.php>
- 4 National Advisory Committee on Immunization (NACI). Vaccine safety and adverse events following immunization. Recommended immunization. In: *Canadian Immunization Guide*. 7th ed. Her Majesty the Queen in Right of Canada, represented by the Minister of Public Works and Government Services Canada. 2006. p. 80-4, 107-12, 117-30, 134-5.
- 5 CDC. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(RR-15):1-48.
- 6 Data on file at Sanofi Pasteur Limited.
- 7 Overbosch D, et al. Combined typhoid fever and hepatitis A vaccine: comparison of immunogenicity and safety to concomitant monovalent vaccine over 3 years. *J Travel Med* 2005;12:319-26.
- 8 Loebermann M, et al. A randomized, open-label study of the immunogenicity and reactogenicity of three lots of a combined typhoid fever/hepatitis A vaccine in healthy adults. *Clin Ther* 2004;26(7):1084-91.
- 9 Zanetti A, et al. Does immunoglobulin interfere with the immunogenicity to Pasteur Merieux inactivated hepatitis A vaccine? *J Hepatol* 1997;26:25-30.
- 10 Dumas R, et al. Safety and immunogenicity of a new inactivated hepatitis A vaccine in concurrent administration with a typhoid fever vaccine or a typhoid fever and yellow fever vaccine. *Adv Therapy* 1997;14(4):160-7.
- 11 Robbins JD, Robbins JB. Re-examination of the protective role of the capsular polysaccharide (Vi antigen) of *Salmonella typhi*. *J Infect Dis* 1984;150:436-49.
- 12 Van Herck K, et al. Mathematical models for assessment of long-term persistence of antibodies after vaccination with two inactivated hepatitis A vaccines. *J Med Virol* 2000;60:1-7.
- 13 Wiedermann G, et al. Inactivated hepatitis A vaccine: long-term antibody persistence. *Vaccine* 1997;15(6-7):612-15.
- 14 Van Herck K and Van Damme P. Inactivated hepatitis A vaccine-induced antibodies: follow-up and estimates of long-term persistence. *J Med Virol* 2001;63(1):1-7.

- 15 Van Damme P, et al. Inactivated hepatitis A vaccine: reactogenicity, immunogenicity, and long-term antibody persistence. *J Med Virol* 1994;44(4):446-51.
- 16 Van Damme P, et al. International Consensus Group on Hepatitis A Virus Immunity. Consensus Statement. Hepatitis A booster vaccination: is there a need? *Lancet* 2003;362(9389):1065-71.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

ViVAXIM®

Combined Purified Vi Polysaccharide Typhoid and Inactivated Hepatitis A Vaccine

Read this carefully before you start taking ViVAXIM®. This leaflet is a summary and will not tell you everything about this product. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about taking ViVAXIM®.

What is ViVAXIM® used for?

ViVAXIM® is a vaccine that is used to prevent typhoid fever and hepatitis A infection. This vaccine may be given to persons 16 years of age and older.

Typhoid fever is an infectious disease spread through food and drink that contain the bacteria (called *Salmonella enterica*, subtype typhi) that cause the illness. It is a serious infection that may be fatal, particularly if not treated promptly.

Hepatitis A is a contagious liver disease that is spread from person to person through drinking water or eating food with the hepatitis A virus (HAV) in it. It is also spread by close personal contact. It is more common in areas of the world with poor sanitation. Hepatitis A can cause a mild illness, but about 1 person in 5 has to be hospitalized and sometimes people die as a result of hepatitis A. Both diseases are more common in areas of the world with poor sanitation.

The majority of persons who are vaccinated with ViVAXIM® will produce enough antibodies to help protect them against these two diseases. However, as with all vaccines, 100% protection cannot be guaranteed.

How does ViVAXIM® work?

ViVAXIM® causes the body to produce its own natural protection against typhoid fever and hepatitis A infection. After you receive the vaccine, your body begins to make substances called antibodies. Antibodies help your body to fight disease. If a vaccinated person comes into contact with one of the germs that cause these diseases, the body is usually ready to destroy it.

What are the ingredients in ViVAXIM®?

Medicinal ingredients: purified *Salmonella typhi* and inactivated hepatitis A virus.

Non-medicinal ingredients: aluminum hydroxide, formaldehyde, neomycin, 2-phenoxyethanol, and polysorbate 80.

ViVAXIM® comes in the following dosage forms:

ViVAXIM® is a liquid vaccine, supplied in a 1 mL pre-filled, dual chamber syringe.

Do not use ViVAXIM® if:

- You have a known severe allergy to any ingredient in the vaccine or its container, or have had a severe allergic reaction after receiving a vaccine that contained similar ingredients.

[To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ViVAXIM®. Talk about any health conditions or problems you may have, including if you:

- **Have a high fever or serious illness.** Wait until you are better to receive the vaccination.
- **Have an allergy to any component of the vaccine or the container.**
- **Have a weakened immune system.** The vaccine may provide you with a lower level of protection than it does for people with healthy immune systems.
- **Have a bleeding disorder or are taking blood thinning medications.** Tell the person giving you the injection about your condition. The injection must be done carefully to prevent excessive bleeding.
- **Are pregnant or breast-feeding.** It is important that you understand the risks and benefits of vaccination. ViVAXIM® should be given to a pregnant or nursing woman only if it is clearly needed. Tell the person giving you the injection if you are pregnant or breast-feeding.
- **Have fainted with a previous injection.** Fainting can occur following vaccination. Appropriate measures should be taken to prevent falling injury.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ViVAXIM®:

- DO NOT mix ViVAXIM® with other vaccines or medicinal products in the same syringe.

How to take ViVAXIM®:

Usual dose:

A single dose of 1 mL is recommended for immunization in persons 16 years of age and older.

Initial protection is provided by one dose of ViVAXIM®. For long-term protection against hepatitis A, a booster vaccination with an inactivated hepatitis A vaccine or ViVAXIM® will be required 6 to 36 months after vaccination with ViVAXIM®. The body does not develop long-term (more than 3 years) protection against typhoid fever and repeat vaccinations are required to maintain protection.

The vaccination should be given in the muscle, preferably in the deltoid (shoulder) region.

Overdose:

If you think you have taken too much ViVAXIM[®], contact a health care professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Not applicable to this vaccine.

What are the possible side effects from using ViVAXIM[®]?

These are not all the possible side effects you may feel when taking ViVAXIM[®]. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of ViVAXIM[®] causing serious harm is extremely small. The small risks associated with ViVAXIM[®] are much less than the risks associated with getting the diseases.

Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well after receiving ViVAXIM[®].

Serious side effects are very rare.

Some people who receive ViVAXIM[®] may have mild side effects such as pain at the injection site, associated with redness and swelling. They may also have fever, headache, dizziness, weakness, muscle aches, or gastrointestinal tract disorders such as nausea, vomiting or diarrhea. These side effects usually go away within a few days.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Suspected Vaccine Adverse Events

For the General Public:

If you suspect you have had a serious or unexpected event following receipt of a vaccine, please ask your healthcare professional to complete the Adverse Events Following Immunization (AEFI) Form and send it to your local health unit in your province/territory.

For Health Care Professionals:

If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local health unit in your province/territory.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018

By toll-free fax: 1-866-844-5931

By email: caefi@phac-aspc.gc.ca

Note: Should you require information related to the management of the adverse events, please contact your health-care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

Storage:

Store ViVAXIM® in a refrigerator at 2° to 8°C (35° to 46°F). **Do not freeze.** Throw the product away if it has been exposed to freezing.

Do not use after the expiration date.

Keep out of reach and sight of children.

If you want more information about ViVAXIM®:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the Sanofi Pasteur Limited website (<http://www.sanofipasteur.ca>), or by calling the Sanofi Pasteur Limited Vaccine Information Service at 1-888-621-1146 (no charge) or at 416-667-2779 (Toronto area). Business hours are 7:30 a.m. to 7:30 p.m. EST Monday to Friday.

This leaflet was prepared by Sanofi Pasteur Limited.

Last revised: September 2015

R4-0915 Canada