AUSTRALIAN PRODUCT INFORMATION – TYPHIM VI™, SALMONELLA TYPHI VI POLYSACCHARIDE

1 NAME OF THE MEDICINE

Typhim VI ™ *Salmonella typhi* VI polysaccharide vaccine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL dose contains:

Salmonella typhi Vi polysaccharide …….25 micrograms

Typhim Vi is a sterile solution, prepared from the purified Vi capsular polysaccharide of *Salmonella typhi* (Ty 2 strain). The purified Vi capsular polysaccharide is diluted in isotonic buffer solution which contains phenol as preservative.

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

The manufacture of this product includes exposure to bovine 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.

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Typhim Vi is indicated for active immunisation against typhoid fever caused by *Salmonella typhi* in individuals 2 years of age and over.

4.2 DOSE AND METHOD OF ADMINISTRATION

A single dose of 0.5 mL for adults is given intramuscularly in the deltoid, and the dose for children is given intramuscularly either in the deltoid or the vastus lateralis. The vaccine should not be injected into the gluteal area or areas where there may be a nerve trunk.

The vaccination dose is the same for adults and children.

TyphimVi should be administered at least 14 days prior to potential exposure to infection with *Salmonella typhi*.

An optimal revaccination schedule has not been established. Revaccination consisting of a single dose every three years for individuals under conditions of repeated or continued exposure to the *Salmonella typhi* organism is recommended at this time.

Product is for single use only and must not be used in more than one individual. Discard any remaining unused contents.

4.3 CONTRAINDICATIONS

Known systemic hypersensitivity reaction to any component of Typhim Vi or a life-threatening reaction after previous administration of the vaccine or vaccine containing the same substance.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As each dose may contain traces of formaldehyde and casein, which are used during vaccine production, caution should be exercised when the vaccine is administered to individuals with hypersensitivity to these substances.

This vaccine provides protection against the risk of infection related to *Salmonella typhi,* but gives no protection against *Salmonella paratyphi* A or B or against *non-typhoidal Salmonellae*.

The immunogenicity of Typhim Vi could be reduced by immunosuppressive treatment or immunodeficiency. In such cases it is recommended to postpone the vaccination until the end of the treatment or resolution of the disease. Nevertheless, vaccination of individuals with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited.

Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

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

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

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

Vaccination should occur at least 2 weeks prior to potential exposure to infection with *Salmonella typhi*.

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

Use in the elderly

Immunogenicity and clinical experience with Typhim Vi in the elderly is limited.

Paediatric use

As with other polysaccharide vaccines, the antibody response may be inadequate in children under 2 years of age.

Effects on laboratory tests

Interference of Typhim Vi with laboratory and/or diagnostic tests has not been studied.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Available data support concomitant use of Typhim Vi with yellow fever vaccine in separate syringes at separate sites. Data concerning use with other vaccines are limited. However, no interaction is anticipated when vaccines are given at separate sites using separate syringes.

Separate injection sites must be used in case of concomitant administration.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Typhim Vi has not been evaluated for the effects on fertility.

Use in pregnancy

Category B2

Animal reproduction studies have not been conducted with Typhim Vi.

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

Adverse event information is derived from clinical trials and worldwide post-marketing experience.

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

Very common:	≥ 1/10 (≥10%)
Common (frequent):	≥ 1/100 and < 1/10 (≥ 1% and < 10%)
Uncommon (infrequent):	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare:	≥ 1/10.000 and < 1/1000 (≥ 0.01% and < 0.1%)
Very rare:	< 1/10.000 (< 0.01%)
Not known	(cannot be estimated from the available data).

Data from clinical studies

In clinical studies, more than 15,000 subjects (all ages) received Typhim Vi either in a single injection or as a second injection.

The most frequently reported adverse events reactions, in all age groups, after administration Typhim Vi were mild injection site pain

In adults from 18 years of age, myalgia and fatigue were the most frequently reported systemic reactions.

In children and adolescents (from 2 to 17 of age), myalgia and headache were the most frequently reported systemic reactions.

The adverse reactions observed during clinical trials were generally of mild to moderate intensity, and appeared with 3 days after vaccination. Most reactions resolved spontaneously within 1 to 3 days after onset.

The table 1 below summarises the frequencies of subjects experiencing at least one solicited adverse reactions that were recorded within 7 days following vaccination in 1435 adults and 97 children and adolescents from 2 to 17 years of age.

Table 1- Frequencies of subjects experiencing at least one solicited adverse reactions that were recorded within 7 days following vaccination

Subjects experiencing at least one:	**Children and Adolescents 2-17 years (N=97)**	**Adults ≥ 18 years (N =1435)**
Adverse Reactions	%	%
General disorders and administration site condition		
Injection site pain	52.6%	75.6%
Injection sire erythema	14.4%	7.7%

Subjects experiencing at least one:	Children and Adolescents 2-17 years (N=97)	Adults ≥ 18 years (N =1435)
Injection site swelling/oedema/induration	16.5%	6.0%
Malaise	6.3%	13.3%
Fever	1.0%	0%
Fatigue/asthenia	4.8%	25.0%
Nervous system disorders		
Headache	13.5%	7.8%
Musculoskeletal and connective tissue disorders		
Myalgia	14.6%	47.1%

N: Number of subject analysed according to safety analyses set.

The table below summarises the frequencies of subjects experiencing at least one unsolicited adverse reactions that were recorded within 28 days following vaccination in 1435 adults and 97 children and adolescents from 2 to 17 years of age.

Table 2- Frequencies of subjects experiencing at least one unsolicited adverse reactions that were recorded within 28 days following vaccination

Subjects experiencing at least one:	Children and Adolescents 2-17 years (N=97)	Adults ≥ 18 years (N =1435)
Adverse Reactions	% [+] - Frequency	% [+] - Frequency
General disorders and administration site condition		
Injection site pain	0%	0.1%

N: Number of subject analysed according to safety analyses set.
[+]: For each reaction, the frequency has been defined by the number of subject experiencing the reaction divided by the number of subjects with available data.

In a U.S. Reimmunisation study, subjects who had received Typhim Vi 27 or 34 months earlier, and subjects who had never previously received a typhoid vaccination, were randomised to placebo or Typhim Vi, in a double blind study. In this study 5/30 (17%) primary immunisation subjects and 10/45 (22%) reimmunisation subjects had an objective local reaction (erythema and/or induration at the site of injection). No severe or unusual side effects were observed. Most subjects reported pain and/or tenderness (pain upon direct pressure). Local adverse experiences were generally limited to the first 48 hours. Results are summarised in Table 3.

Table 3 –U.S reimmunisation study, subjects presenting with local and systemic reactions within 48 hours after immunization with Typhim Vi.

REACTIONS	Number with Adverse Reactions (%)		
	Placebo (N=32)	First Immunisation (N=30)	Reimmunisation (N=45*)
Local			
Tenderness	2 (6%)	28 (93%)	44 (98%)
Pain (upon direct pressure)	1 (3%)	13 (43%)	25 (56%)
Induration	0	5 (17%)	8 (18%)
Erythema	0	1 (3%)	5 (11%)
Systemic			
Malaise	1 (3%)	11 (37%)	11 (24%)
Headache	5 (16%)	8 (27%)	5 (11%)
Myalgia	0	2 (7%)	1 (2%)
Nausea	0	1 (3%)	1 (2%)
Diarrhoea	0	0	1 (2%)
Feverish (subjective)	0	3 (10%)	2 (4%)
Fever ≥ 38°C	1 (3%)	0	1 (2%)
Vomiting	0	0	0

** At 27 or 34 months following a previous dose given in different studies.*

Data from Post-Marketing Surveillance

Based on spontaneous reporting, the following additional adverse events have been reported during the commercial use of Typhim Vi. These events have been very rarely reported, however exact incidence rates cannot be calculated precisely.

Immune System Disorder

- Anaphylactic/anaphylactoid reactions, including shock; serum sickness

Skin and Subcutaneous Tissue Disorders:

- Allergic type reactions such as rash, pruritus, urticaria

Gastrointestinal Disorders:

- Nausea, vomiting, diarrhoea, abdominal pain

Musculoskeletal and Connective Tissue Disorders:

- Arthralgia

Respiratory Thoracic and Mediastinal Disorders

- Asthma

Nervous System Disorders:

- Vasovagal syncope

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Typhoid Vaccine, ATC code: J07AP03

Mechanism of action

This vaccine contains purified Vi capsular polysaccharide of *Salmonella typhi* (Ty 2 strain). Antibody sero-conversion is observed in over 90% of recipients 28 days after a single dose. Antibodies appear after approximately 7 to 15 days and reach peak values around 28 to 35 days after the injection. Persistence of the antibody response is at least 3 years. Protection is achieved in 60-80% of vaccinees during the first year and in 50-77% during the next 2 years.

Clinical trials

Two formulations were utilized in studies of the typhoid Vi polysaccharide vaccine. These included the liquid formulation which is identical to Typhim Vi and lyophilised formulation. The protective efficacy of each of these formulations of the typhoid Vi polysaccharide vaccine was assessed independently in two trials conducted in areas where typhoid fever is endemic. A single intramuscular dose of 25 micrograms was used in these efficacy studies.

A randomised double-blind controlled trial with Typhim Vi (liquid formulation) was conducted in five villages west of Katmandu, Nepal. There were 6,908 vaccinated subjects: 3,454 received Typhim Vi and 3,454 in the control group received a 23-valent pneumococcal polysaccharide vaccine. Of the 6,908 subjects, 6,439 subjects were in the target population of 5 to 44 years of age. In addition, 165 children ages 2 to 4 years and 304 adults over 44 years of age were included in the study. The overall protective efficacy of Typhim Vi was 74% (95% confidence interval (CI): 49% to 87%) for blood culture confirmed cases of typhoid fever during 20 months of post-vaccination follow-up.

The protective efficacy of the typhoid Vi polysaccharide vaccine, lyophilised formulation, was evaluated in a randomised double-blind controlled trial conducted in South Africa. There were 11,384 vaccinated children 5 to 15 years of age; 5,692 children received the Vi capsular

polysaccharide vaccine and 5,692 in the control group received meningococcal polysaccharide (Groups A+C) vaccine. The protective efficacy for the Vi capsular polysaccharide (lyophilised formulation) group for blood culture confirmed cases of typhoid fever was 55% (95% CI: 30% to 70%) overall during 3 years of post-vaccination follow-up, and was 61%, 52% and 50%, respectively, for years 1, 2, and 3. Vaccination was associated with an increase in anti-Vi antibodies as measured by radioimmunoassay (RIA) and enzyme-linked immunosorbent assay. Antibody levels remained elevated at 6 and 12 months post-vaccination.

An increase in serum anti-capsular antibodies is thought to be the basis of protection provided by Typhim Vi. However, a specific correlation of post-vaccination antibody levels with subsequent protection is not available and the level of Vi antibody that will provide protection has not been determined. Also, limitations exist for comparing immunogenicity. In endemic regions (Nepal, South Africa, Indonesia) where trials were conducted, pre-vaccination geometric mean antibody levels suggest that infection with *S. typhi* has previously occurred in a large percentage of the vaccinees. In these populations, specific antibody levels increased four-fold or greater in 68% to 87.5% of older children and adult subjects following vaccination. For 43 persons 15 to 44 years of age in the Nepal pilot study, geometric mean specific antibody levels pre- and 3 weeks post-vaccination were, respectively, 0.38 and 3.68 μg antibody/mL by RIA; 79% had a four-fold or greater rise in Vi antibody levels.

Immunogenicity and safety trials were conducted in a racially mixed US population. A single dose of Typhim Vi vaccine induced a four-fold or greater increase in antibody levels in 88% and 96% of this adult population for 2 studies, respectively, following vaccination.

A double-blind randomised controlled trial testing the safety and immunogenicity of Typhim Vi was performed in 175 Indonesian children. The percentage of 2- to 5-year-old children achieving a four-fold or greater increase in antibody levels at 4 weeks post-vaccination was 96.3% (52/54) (95% CI: 87.3% to 99.6%), and in the study subset of 2-year-old children was 94.4% (17/18) (95% CI: 72.7% to 99.9%). The geometric mean levels (μg antibody/mL, by RIA) for the 2-to 5-year-old children and the subset of 2-year-olds were, respectively, 5.81 (4.36 to 7.77) and 5.76 (3.48 to 9.53).

In an U.S. Reimmunisation Study, adults previously immunised with Typhim Vi in other studies were reimmunised with a 25 micrograms dose at 27 or 34 months after the primary dose. Data on antibody response to primary immunisation, decline following primary immunisation, and response to reimmunisation are presented in Table 1. Antibody levels attained following reimmunisation at 27 or 34 months after the primary dose were similar to levels attained following the primary immunisation. This response is typical for a T-cell independent polysaccharide vaccine in that reimmunisation does not elicit higher antibody levels than primary immunisation.

Table 4- US studies in 18 to 40 years old adults: kinetics and persistence of Vi antibody * response to primary immunization with Typhim Vi, and response to reimmunisation at 27 or 34 months.

	Pre DOSE 1	1 Month	11 Months	18 Months	27 Months	34 Months	1 Month POST-REIMMUNISATION

GROUP 1 [a]							
N	43	43	39	ND[c]	43	ND	43
Level*	0.19	3.01	1.97		1.07 [d]		3.04
95% CI	(0.14-0.26)	(2.22-4.06)	(1.31-3.00)		(0.71-1.62)		(2.17-4.26)
GROUP 2[b]							
N	12	12	ND	10	ND	12	12
Level	0.14	3.78		1.21		0.76 [d]	3.31
95% CI	(0.11-0.18)	(2.18-6.56)		(0.63-2.35)		(0.37-1.55)	(1.61-6.77)

**µg antibody/mL by RIA.*
[a]Group 1: Reimmunised at 27 months following primary immunisation.
[b]Group 2: Reimmunised at 34 months following primary immunisation.
[c]Not Done.
[d]Antibody levels pre-reimmunization.
[e]Includes available data from all reimmunized subjects (subjects initially randomized to TYPHIM Vi, and subjects initially randomized to placebo who received open label TYPHIM Vi two weeks later).

5.2 PHARMACOKINETIC PROPERTIES

No data available.

5.3 PRECLINICAL SAFETY DATA

5.3.1 Genotoxicity

Typhim Vi has not been evaluated for the genotoxic potential.

5.3.2 Carcinogenicity

Typhim Vi has not been evaluated for the carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Phenol as preservative
- Sodium chloride
- Dibasic sodium phosphate dihydrate
- Monobasic sodium phosphate dihydrate

- Water for injection

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2ºC to 8ºC. Refrigerate. Do not freeze. Product that has been exposed to freezing should not be used. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Single dose pre-filled syringe (0.5ml) with separate needle.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

09 October 2000

10 DATE OF REVISION

14 April 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Change in presentation
8	Sponsor Office Relocation