

AUSTRALIAN PRODUCT INFORMATION

NAME OF THE MEDICINE

TYPHIM VI™

Salmonella typhi Vi polysaccharide vaccine

DESCRIPTION

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. The vaccine is a clear, colourless solution. Each single dose of 0.5 mL is formulated to contain 0.025 milligrams of purified Vi capsular polysaccharide, preserved with phenol (less than 1.25 mg per dose). The isotonic buffer solution contains 4.15 mg of sodium chloride, 0.065 mg of sodium phosphate dibasic dihydrate and 0.023 mg of sodium phosphate monobasic dihydrate.

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.

PHARMACOLOGY

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

Immunogenicity

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 µg 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 µg 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 1: US STUDIES IN 18 TO 40-YEAR-OLD ADULTS: KINETICS AND PERSISTENCE OF Vi ANTIBODY* RESPONSE TO PRIMARY IMMUNIZATION WITH TYPHIM Vi, AND RESPONSE TO REIMMUNIZATION AT 27 OR 34 MONTHS.

	Pre DOSE 1	1 Month	11 Months	18 Months	27 Months	34 Months	1 Month POST-REIMMUNIZATION ^e
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.

^aGroup 1: Reimmunised at 27 months following primary immunisation.

^bGroup 2: Reimmunised at 34 months following primary immunisation.

^cNot Done.

^dAntibody levels pre-reimmunization.

^eIncludes 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).

INDICATIONS

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

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.

PRECAUTIONS

As each dose may contain traces of formaldehyde, which is used during vaccine production, caution should be exercised when the vaccine is administered to individuals with hypersensitivity to this product.

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.

Individuals with impaired immune system, such as those with an immunosuppressive disease or receiving immunosuppressive drugs may not develop the expected antibody response to TYPHIM Vi. 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.

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.

TYPHIM Vi protects against typhoid fever caused by *Salmonella typhi*. Protection is not conferred against paratyphoid fever or illness caused by non-invasive Salmonellae. The importance of scrupulous attention to personal, food and water hygiene must be emphasised for all persons at risk of typhoid fever.

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.

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.

Paediatric use

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

Use in the elderly

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

Genotoxicity

TYPHIM Vi has not been evaluated for the genotoxic potential.

Carcinogenicity

TYPHIM Vi has not been evaluated for the carcinogenic potential.

Effects on laboratory tests

Interference of TYPHIM Vi with laboratory tests has not been studied.

INTERACTIONS WITH OTHER MEDICINES

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.

ADVERSE EFFECTS

Clinical Trials Experience

Adverse reactions from a trial in Indonesia investigating safety in children receiving TYPHIM Vi, aged 1 to 12 years, are summarised in Table 2.

TABLE 2: PERCENTAGE OF INDONESIAN CHILDREN ONE TO TWELVE YEARS OF AGE PRESENTING WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 48 HOURS AFTER THE FIRST IMMUNIZATION WITH TYPHIM Vi.	
REACTIONS	Number with Adverse Reactions (%) N=175

Local	
Soreness	23 (13.0%)
Pain	25 (14.3%)
Erythema	12 (6.9%)
Induration	5 (2.9%)
Impaired Limb Use	0
Systemic	
Feverishness (subjective)	5 (2.9%)
Headache	0
Decreased Activity	3 (1.7%)

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. REIMMUNIZATION 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 $\geq 38^{\circ}\text{C}$	1 (3%)	0	1 (2%)
Vomiting	0	0	0

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

Adverse Reactions 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.

General Disorders and Administration Site Conditions

- Malaise, fatigue

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, myalgia

Respiratory Thoracic and Mediastinal Disorders

- Asthma

Nervous System Disorders:

- Vasovagal syncope

DOSAGE AND 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.

TYPHIM Vi 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 *S. 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.

OVERDOSAGE

There is no data on overdose of TYPHIM Vi.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Single dose pre-filled syringe, unit pack.

Storage

Store at 2°C-8°C. Refrigerate. Do not freeze. Product that has been exposed to freezing should not be used. Do not use after expiration date.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

09 October 2000

DATE OF MOST RECENT AMENDMENT

3 February 2016