

1 AHFS Category: 80:12

Typh

TYPHOID VI POLYSACCHARIDE VACCINE
TYPHIM VI®

Rx only



2

3 **DESCRIPTION**

4 Typhim Vi®, Typhoid Vi Polysaccharide Vaccine, produced by Sanofi Pasteur SA, for
5 intramuscular use, is a sterile solution containing the cell surface Vi polysaccharide extracted
6 from *Salmonella enterica* serovar *Typhi*, *S typhi* Ty2 strain. The organism is grown in a semi-
7 synthetic medium. Casein derived raw materials are used early in manufacturing during the
8 fermentation process. The capsular polysaccharide is precipitated from the concentrated culture
9 supernatant by the addition of hexadecyltrimethylammonium bromide, and the product is purified
10 by differential centrifugation and precipitation. Each 0.5 mL dose may contain residual amounts
11 of formaldehyde (not more than 100 mcg) used for the inactivation of the bacterial culture. The
12 potency of the purified polysaccharide is assessed by molecular size and O-acetyl content. Phenol,
13 0.25%, is added as a preservative. The vaccine contains residual polydimethylsiloxane or fatty-
14 acid ester-based antifoam. The vaccine is a clear, colorless solution. Each dose of 0.5 mL is
15 formulated to contain 25 mcg of purified Vi polysaccharide in a colorless isotonic phosphate
16 buffered saline (pH 7 ± 0.3), 4.150 mg of Sodium Chloride, 0.065 mg of Disodium Phosphate,
17 0.023 mg of Monosodium Phosphate, and 0.5 mL of Sterile Water for Injection.

18

19 **CLINICAL PHARMACOLOGY**

1 Typhoid fever is an infectious disease caused by *S typhi*. Humans are the only natural host and
2 reservoir for *S typhi*; infections result from the consumption of food or water that has been
3 contaminated by the excretions of an acute case or a carrier. *S typhi* organisms efficiently invade
4 the human intestinal mucosae ultimately leading to bacteremia; following a typical 10- to 14-day
5 incubation period, a systemic illness occurs. The clinical presentation of typhoid fever exhibits a
6 broad range of severity and can be debilitating. Classical cases have fever, myalgia, anorexia,
7 abdominal discomfort and headaches; the fever increases step-wise over a period of days and then
8 may remain at 102°F to 106°F over 10 to 14 days before decreasing in a step-wise manner. Skin
9 lesions known as rose spots may be present. Constipation is common in older children and adults,
10 while diarrhea may occur in younger children. Among the less common but most severe
11 complications are intestinal perforation and hemorrhage, and death. The course is typically more
12 severe without appropriate antimicrobial therapy. The case fatality rate was reported to be
13 approximately 10% to 20% in the pre-antibiotic era. (1) (2) (3) During the period of 1983 to 1991
14 in the US, the case fatality rate reported to the Centers for Disease Control and Prevention (CDC)
15 was 0.2% (9/4010). (4) Infection of the gallbladder can lead to the chronic carrier state.

16

17 Typhoid fever is still endemic in many countries of the world where it is predominantly a disease
18 of school-age children and may be a major public health problem. Most cases of typhoid fever in
19 the US are thought to be acquired during foreign travel. During the periods of 1975 to 1984 and
20 1983 to 1984, respectively, 62% and 70% of the cases of typhoid fever reported to the CDC were
21 acquired during foreign travel; this compares to 33% of cases during 1967-1972. (5)

22

1 In 1992, 414 cases of typhoid fever were reported to the CDC. Of these 414 cases, 1 (0.2%) case
2 occurred in an infant under one year of age; 77 (18.6%) cases occurred in persons one to nine
3 years of age; 81 (19.6%) cases occurred in persons 10 to 19 years of age; 251 (60.6%) cases
4 occurred in individuals ≥ 20 years of age; the age was not available for 4 (1%) cases. One death
5 was reported in 1991. (4) Domestic surveillance could underestimate the risk of typhoid fever in
6 travelers since the disease is unlikely to be reported for persons who received diagnosis and
7 treatment overseas. (6)

8
9 Approximately 2% to 4% of acute typhoid fever cases develop into a chronic carrier state. The
10 chronic carrier state occurs more frequently with advanced age, and among females than males. (2
11) (7) These non-symptomatic carriers are the natural reservoir for *S typhi* and can serve to
12 maintain the disease in its endemic state or to directly infect new individuals. Outbreaks of
13 typhoid fever are often traced to food handlers who are asymptomatic carriers. (8)

14
15 Two formulations were utilized in studies of the Typhoid Vi Polysaccharide Vaccine. These
16 included the liquid formulation which is identical to Typhim Vi vaccine and a lyophilized
17 formulation.

18
19 The protective efficacy of each of these formulations of the Typhoid Vi Polysaccharide Vaccine
20 was assessed independently in two trials conducted in areas where typhoid fever is endemic. A
21 single intramuscular dose of 25 mcg was used in these efficacy studies. A randomized double-
22 blind controlled trial with Typhim Vi vaccine (liquid formulation) was conducted in five villages
23 west of Katmandu, Nepal. There were 6,908 vaccinated subjects: 3,454 received Typhim Vi

1 vaccine and 3,454 in the control group received a 23-valent pneumococcal polysaccharide
2 vaccine. Of the 6,908 subjects, 6,439 subjects were in the target population of 5 to 44 years of
3 age. In addition, 165 children ages 2 to 4 years and 304 adults over 44 years of age were included
4 in the study. The overall protective efficacy of Typhim Vi vaccine was 74% (95% confidence
5 interval (CI): 49% to 87%) for blood culture confirmed cases of typhoid fever during 20 months
6 of post-vaccination follow-up. (9) (10) (11)

7

8 The protective efficacy of the Typhoid Vi Polysaccharide Vaccine, lyophilized formulation, was
9 evaluated in a randomized double-blind controlled trial conducted in South Africa. There were
10 11,384 vaccinated children 5 to 15 years of age; 5,692 children received the Vi capsular
11 polysaccharide vaccine and 5,692 in the control group received Meningococcal Polysaccharide
12 (Groups A+C) Vaccine. The protective efficacy for the Vi capsular polysaccharide (lyophilized
13 formulation) group for blood culture confirmed cases of typhoid fever was 55% (95% CI: 30% to
14 70%) overall during 3 years of post-vaccination follow-up, and was 61%, 52% and 50%,
15 respectively, for years 1, 2, and 3. Vaccination was associated with an increase in anti-Vi
16 antibodies as measured by radioimmunoassay (RIA) and enzyme-linked immunosorbent assay.
17 Antibody levels remained elevated at 6 and 12 months post-vaccination. (11) (12)

18

19 Because of the low incidence of typhoid fever, efficacy studies were not feasible in a US
20 population.

21

22 Controlled comparative efficacy studies of Typhim Vi vaccine and other types of typhoid
23 vaccines have not been performed.

1

2 An increase in serum anti-capsular antibodies is thought to be the basis of protection provided by
3 Typhim Vi vaccine. However, a specific correlation of post-vaccination antibody levels with
4 subsequent protection is not available, and the level of Vi antibody that will provide protection
5 has not been determined. Also, limitations exist for comparing immunogenicity results from
6 subjects in endemic areas, where some subjects have baseline serological evidence of prior *S typhi*
7 exposure, to naive populations such as most American travelers.

8

9 In endemic regions (Nepal, South Africa, Indonesia) where trials were conducted, pre-vaccination
10 geometric mean antibody levels suggest that infection with *S typhi* had previously occurred in a
11 large percentage of the vaccinees. In these populations, specific antibody levels increased four-
12 fold or greater in 68% to 87.5% of older children and adult subjects following vaccination. For 43
13 persons 15 to 44 years of age in the Nepal pilot study, geometric mean specific antibody levels
14 pre- and 3 weeks post-vaccination were, respectively, 0.38 and 3.68 mcg antibody/mL by RIA;
15 79% had a four-fold or greater rise in Vi antibody levels. (9) (12)

16

17 Immunogenicity and safety trials were conducted in an adult US population. A single dose of
18 Typhim Vi vaccine induced a four-fold or greater increase in antibody levels in 88% and 96% of
19 this adult population for 2 studies, respectively, following vaccination (see [Table 1](#)). (10) (13)

20

1 **Table 1 (10) (13): Vi ANTIBODY LEVELS IN US ADULTS 18 TO 40 YEARS OF AGE**
2 **GIVEN TYPHIM Vi VACCINE**

	N	GEOMETRIC MEAN ANTIBODY LEVELS (mcg antibody/mL by RIA)		% ≥4 FOLD INCREASE (95% CI)
		Pre (95% CI)	Post (4 weeks) (95% CI)	
Trial 1 (1 lot)	54	0.16 (0.13 to 0.21)	3.23 (2.59 to 4.03)	96% (52/54) (87% to 100%)
Trial 2 (2 lots combined)	97	0.17 (0.14 to 0.21)	2.86 (2.26 to 3.62)	88% (85/97) (81% to 94%)

3

4 No studies of safety and immunogenicity have been conducted in US children. A double-blind
5 randomized controlled trial evaluating the safety and immunogenicity of Typhim Vi vaccine was
6 performed in 175 Indonesian children. The percentage of 2- to 5-year-old children achieving a
7 four-fold or greater increase in antibody levels at 4 weeks post-vaccination was 96.3% (52/54)
8 (95% CI: 87.3% to 99.6%), and in the study subset of 2-year-old children was 94.4% (17/18)
9 (95% CI: 72.7% to 99.9%). The geometric mean antibody levels (mcg antibody/mL by RIA) for
10 the 2-to 5-year-old children and the subset of 2-year-olds were, respectively, 5.81 (4.36 to 7.77)
11 and 5.76 (3.48 to 9.53). (10) (11)

12

13 In the US Reimmunization Study, adults previously immunized with Typhim Vi vaccine in other
14 studies were reimmunized with a 25 mcg dose at 27 or 34 months after the primary dose. Data on
15 antibody response to primary immunization, decline following primary immunization, and
16 response to reimmunization are presented in [Table 2](#). Antibody levels attained following

1 reimmunization at 27 or 34 months after the primary dose were similar to levels attained
 2 following the primary immunization. (10) (13) This response is typical for a T-cell independent
 3 polysaccharide vaccine in that reimmunization does not elicit higher antibody levels than primary
 4 immunization. The safety of reimmunization was also evaluated in this study (see [ADVERSE](#)
 5 [REACTIONS](#) section).

6

7 **Table 2 (10) (13): US STUDIES IN 18- TO 40-YEAR-OLD ADULTS: KINETICS AND**
 8 **PERSISTENCE OF Vi ANTIBODY* RESPONSE TO PRIMARY IMMUNIZATION**
 9 **WITH TYPHIM Vi VACCINE, AND RESPONSE TO REIMMUNIZATION AT 27 OR 34**
 10 **MONTHS**

	PRE-DOSE 1	1 MONTH	11 MONTHS	18 MONTHS	27 MONTHS	34 MONTHS	1 MONTH POST-REIMMUNIZATION [†]
GROUP 1 [†]							
N	43	43	39	ND [§]	43	ND	43
Level*	0.19	3.01	1.97		1.07		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 [‡]							
N	12	12	ND	10	ND	12	12
Level	0.14	3.78		1.21		0.76	3.31
95% CI	(0.11-0.18)	(2.18-6.56)		(0.63-2.35)		(0.37-1.55)	(1.61-6.77)

11 * mcg antibody/mL by RIA

12 † Group 1: Reimmunized at 27 months following primary immunization.

13 ‡ Group 2: Reimmunized at 34 months following primary immunization.

14 § Not Done.

15 || Antibody levels pre-reimmunization.

¶ Includes available data from all reimmunized subjects (subjects initially randomized to Typhim Vi vaccine, and subjects initially randomized to placebo who received open label Typhim Vi vaccine two weeks later).

Concurrently Administered Vaccines

Concomitant Administration of Typhim Vi and Menactra vaccine

In a double-blind, randomized, controlled clinical trial, 945 participants aged 18 through 55 years received Typhim Vi and Menactra vaccines concomitantly (N=469), or Typhim Vi vaccine followed one month later by Menactra vaccine (N=476). Sera were obtained approximately 28 days after each respective vaccination. The antibody response to Typhim Vi vaccine and to Menactra vaccine components were similar between groups.

INDICATIONS AND USAGE

Typhim Vi vaccine is indicated for active immunization for the prevention of typhoid fever caused by *S typhi* and is approved for use in persons two years of age or older.

Immunization with Typhim Vi vaccine should occur at least two weeks prior to expected exposure to *S typhi*.

Typhim Vi vaccine is not indicated for routine immunization of individuals in the United States (US). (14)

Selective immunization against typhoid fever is recommended under the following circumstances:

1) travelers to areas where a recognized risk of exposure to typhoid exists, particularly ones who will have prolonged exposure to potentially contaminated food and water, 2) persons with

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1 intimate exposure (ie, continued household contact) to a documented typhoid carrier, and 3)
2 workers in microbiology laboratories who frequently work with *S typhi*. (14)

3

4 Typhoid vaccination is not required for international travel, but is recommended for travelers to
5 such areas as Africa, Asia, and Central and South America where there is a recognized risk of
6 exposure to *S typhi*. Current CDC advisories should be consulted with regard to specific locales.
7 Vaccination is particularly recommended for travelers who will have prolonged exposure to
8 potentially contaminated food and water. However, even travelers who have been vaccinated
9 should use caution in selecting food and water. (15)

10

11 There is no evidence to support the use of typhoid vaccine to control common source outbreaks,
12 disease following natural disaster or in persons attending rural summer camps. (14)

13

14 An optimal reimmunization schedule has not been established. Reimmunization every two years
15 under conditions of repeated or continued exposure to the *S typhi* organism is recommended at
16 this time.

17

18 For recommended primary immunization and reimmunization see [DOSAGE AND](#)
19 [ADMINISTRATION](#) section.

20

21 Typhim Vi vaccine should not be used to treat a patient with typhoid fever or a chronic typhoid
22 carrier.

23

1 **CONTRAINDICATIONS**

2 TYPHIM Vi VACCINE IS CONTRAINDICATED IN PATIENTS WITH A HISTORY OF
3 HYPERSENSITIVITY TO ANY COMPONENT OF THIS VACCINE.

4

5 **WARNINGS**

6 Allergic reactions have been reported rarely in the post-marketing experience (see [ADVERSE](#)
7 [REACTIONS](#) section).

8

9 The safety and immunogenicity of Typhim Vi vaccine in children under two years of age has not
10 been established. As with other polysaccharide vaccines, the antibody response may be
11 inadequate. The decision whether to vaccinate children under 2 years of age depends upon the risk
12 incurred by the child on the basis of the epidemiological context.

13

14 Typhim Vi vaccine provides protection against the risk of infection related to *Salmonella typhi*,
15 but gives no protection against *Salmonella paratyphi A* or *B*, non-*S typhi* species of *Salmonella*
16 *enterica* serovar *Typhi*, or other bacteria that cause enteric disease.

17

18 If the vaccine is used in persons deficient in producing antibodies, whether due to genetic defect,
19 immunodeficiency disease, or immunosuppressive therapy, the expected immune response may
20 not be obtained. This includes patients with asymptomatic or symptomatic HIV-infection, severe
21 combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered

1 immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an
2 immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites
3 or radiation. (16)

4

5 As with any vaccine, vaccination with Typhim Vi vaccine may not protect 100% of individuals.

6

7 **PRECAUTIONS**

8 **General**

9 Care is to be taken by the health-care provider for the safe and effective use of Typhim Vi
10 vaccine.

11

12 **EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE**
13 **FOLLOWING IMMUNIZATION SHOULD AN ANAPHYLACTIC OR OTHER ALLERGIC**
14 **REACTIONS OCCUR DUE TO ANY COMPONENT OF THE VACCINE.**

15

16 Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse
17 reactions. This includes a review of the patient's history with respect to possible hypersensitivity
18 to the vaccine or similar vaccines.

19

20 Acute infection or febrile illness may be reason for delaying use of Typhim Vi vaccine except
21 when, in the opinion of the physician, withholding the vaccine entails a greater risk.

22

1 Syncope (fainting) has been reported following vaccination with Typhim Vi. Procedures should
2 be in place to prevent falling injury and manage syncopal reactions.

3

4 A separate, sterile syringe and needle or a sterile disposable unit must be used for each patient to
5 prevent the transmission of infectious agents from person to person. Needles should not be
6 recapped and should be properly disposed.

7

8 Do not administer intravenously.

9

10 Safety and immunogenicity data from controlled trials are not available for Typhim Vi vaccine
11 following previous immunization with whole-cell typhoid or live, oral typhoid vaccine (see
12 [ADVERSE REACTIONS](#) section).

13

14 **INFORMATION FOR VACCINE RECIPIENTS OR PARENTS/GUARDIANS**

15 Before administration, healthcare providers should inform patients, parents or guardians of the
16 benefits and risks of immunization with Typhim Vi vaccine.

17

18 Prior to administration of Typhim Vi vaccine, healthcare providers should ask patients, parents
19 and guardians about the recent health status of the patient to be immunized.

20

21 Typhim Vi vaccine is indicated in persons traveling to endemic or epidemic areas. Current CDC
22 advisories should be consulted with regard to specific locales.

23

1 Travelers should take all necessary precautions to avoid contact with or ingestion of contaminated
2 food and water.

3

4 One dose of vaccine should be given at least 2 weeks prior to expected exposure.

5

6 Reimmunization consisting of a single-dose for US travelers every two years under conditions of
7 repeated or continued exposure to the *S typhi* organism is recommended at this time. (14)

8

9 As part of the child's or adult's immunization record, the date, lot number, and manufacturer of the
10 vaccine administered should be recorded. (17)

11

12 **DRUG INTERACTIONS**

13 There are no known interactions of Typhim Vi vaccine with drugs or foods.

14

15 **Concomitant Vaccine Administration**

16 Typhim Vi was concomitantly administered with Menactra vaccine in individuals 18 through 55
17 years of age (see [CLINICAL PHARMACOLOGY](#) and [ADVERSE REACTIONS](#)).

18

19 No studies have been conducted in the US to evaluate interactions or immunological interference
20 between the concurrent use of Typhim Vi vaccine and drugs (including antibiotics and
21 antimalarial drugs), immune globulins or other vaccines (including common travelers vaccines
22 such as tetanus, poliomyelitis, hepatitis A, and yellow fever).

23

1

2 Typhim Vi vaccine must not be mixed with any vaccine in the same syringe. Separate injection
3 sites should be used in case of concomitant administration.

4

5 **CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**

6 Typhim Vi vaccine has not been evaluated for its carcinogenic potential, mutagenic potential or
7 impairment of fertility.

8

9 **PREGNANCY CATEGORY C**

10 Animal reproduction studies have not been conducted with Typhim Vi vaccine. It is not known
11 whether Typhim Vi vaccine can cause fetal harm when administered to a pregnant woman or can
12 affect reproduction capacity. Typhim Vi vaccine should be given to a pregnant woman only if
13 clearly needed. (14)

14

15 When possible, delaying vaccination until the second or third trimester to minimize the possibility
16 of teratogenicity is a reasonable precaution. (18)

17

18 **NURSING MOTHERS**

19 It is not known whether Typhim Vi vaccine is excreted in human milk. Because many drugs are
20 excreted in human milk, caution should be exercised when Typhim Vi vaccine is administered to
21 a nursing woman.

22

23 There is no data on the use of this product in nursing mothers.

24

1 **PEDIATRIC USE**

2 Safety and effectiveness of Typhim Vi vaccine have been established in children 2 years of age
3 and older. (10) (11) (See [DOSAGE AND ADMINISTRATION](#) section.) FOR CHILDREN
4 BELOW THE AGE OF 2 YEARS, SAFETY AND EFFECTIVENESS HAVE NOT BEEN
5 ESTABLISHED.

6

7 **ADVERSE REACTIONS**

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

10

11 **DATA FROM CLINICAL TRIALS**

12 Because clinical trials are conducted under widely varying conditions, adverse reactions rates
13 observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials
14 of another vaccine and may not reflect the rates observed in practice. The adverse reaction
15 information from clinical trials does, however, provide a basis for identifying the adverse events
16 that appear to be related to vaccine use and for approximating rates.

17

18 Safety of Typhim Vi vaccine, the US licensed liquid formulation, has been assessed in clinical
19 trials in more than 4,000 subjects both in countries of high and low endemicity. In addition, the
20 safety of the lyophilized formulation has been assessed in more than 6,000 individuals. The
21 adverse reactions were predominately minor and transient local reactions. Local reactions such as
22 injection site pain, erythema, and induration almost always resolved within 48 hours of
23 vaccination. Elevated oral temperature, above 38°C (100.4°F), was observed in approximately 1%

1 of vaccinees in all studies. No serious or life-threatening systemic events were reported in these
 2 clinical trials. (10) (11)
 3
 4 Adverse reactions from two trials evaluating Typhim Vi vaccine lots in the US (18- to 40-year-old
 5 adults) are summarized in [Table 3](#). No severe or unusual side effects were observed. Most
 6 subjects reported pain and/or tenderness (pain upon direct pressure). Local adverse experiences
 7 were generally limited to the first 48 hours. (10) (11)
 8

9 **Table 3 (10) (11): PERCENTAGE OF 18- TO 40-YEAR-OLD US ADULTS PRESENTING**
 10 **WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 48 HOURS AFTER THE FIRST**
 11 **IMMUNIZATION WITH TYPHIM Vi VACCINE**

REACTION	Trial 1 Placebo N = 54	Trial 1 Typhim Vi vaccine N = 54 (1 Lot)	Trial 2 Typhim Vi vaccine N = 98 (2 Lots combined)
Local			
Tenderness	7 (13.0%)	53 (98.0%)	95 (96.9%)
Pain	4 (7.4%)	22 (40.7%)	26 (26.5%)
Induration	0	8 (14.8%)	5 (5.1%)
Erythema	0	2 (3.7%)	5 (5.1%)
Systemic			
Malaise	8 (14.8%)	13 (24.0%)	4 (4.1%)
Headache	7 (13.0%)	11 (20.4%)	16 (16.3%)

REACTION	Trial 1 Placebo N = 54	Trial 1 Typhim Vi vaccine N = 54 (1 Lot)	Trial 2 Typhim Vi vaccine N = 98 (2 Lots combined)
Myalgia	0	4 (7.4%)	3 (3.1%)
Nausea	2 (3.7%)	1 (1.9%)	8 (8.2%)
Diarrhea	2 (3.7%)	0	3 (3.1%)
Feverish (subjective)	0	6 (11.1%)	3 (3.1%)
Fever $\geq 100^{\circ}\text{F}$	0	1 (1.9%)	0
Vomiting	0	1 (1.9%)	0

1

2 No studies were conducted in US children. Adverse reactions from a trial in Indonesia in children
3 one to twelve years of age are summarized in [Table 4](#). (10) (11) No severe or unusual side effects
4 were observed.

5

6 **Table 4 (10) (11): PERCENTAGE OF INDONESIAN CHILDREN ONE TO TWELVE**
7 **YEARS OF AGE PRESENTING WITH LOCAL OR SYSTEMIC REACTIONS WITHIN**
8 **48 HOURS AFTER THE FIRST IMMUNIZATION WITH TYPHIM Vi VACCINE**

REACTIONS	N = 175
Local	
Soreness	23 (13.0%)
Pain	25 (14.3%)
Erythema	12 (6.9%)
Induration	5 (2.9%)

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REACTIONS	N = 175
Impaired Limb Use	0
Systemic	
Feverishness*	5 (2.9%)
Headache	0
Decreased Activity	3 (1.7%)

1 * Subjective feeling of fever.

2

3 In the US Reimmunization Study, subjects who had received Typhim Vi vaccine 27 or 34 months
4 earlier, and subjects who had never previously received a typhoid vaccination, were randomized
5 to placebo or Typhim Vi vaccine, in a double-blind study. Safety data from the US

6 Reimmunization Study are presented in [Table 5](#). (10) (11) (13) In this study 5/30 (17%) primary
7 immunization subjects and 10/45 (22%) reimmunization subjects had a local reaction. No severe
8 or unusual side effects were observed. Most subjects reported pain and/or tenderness (pain upon
9 direct pressure). Local adverse experiences were generally limited to the first 48 hours. (10) (11)

10 (13)

11

1 **Table 5 (10) (11) (13): US REIMMUNIZATION STUDY, SUBJECTS PRESENTING**
 2 **WITH LOCAL AND SYSTEMIC REACTIONS WITHIN 48 HOURS AFTER**
 3 **IMMUNIZATION WITH TYPHIM Vi VACCINE**

REACTION	PLACEBO (N = 32)	FIRST IMMUNIZATION (N = 30)	REIMMUNIZATION (N = 45*)
Local			
Tenderness	2 (6%)	28 (93%)	44 (98%)
Pain	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%)
Diarrhea	0	0	1 (2%)
Feverish (subjective)	0	3 (10%)	2 (4%)
Fever ≥100°F	1 (3%)	0	1 (2%)
Vomiting	0	0	0

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

5

6 **Solicited Injection Site and Systemic Reactions When Given With Menactra Vaccine**

7 The majority (70%-77%) of solicited injection site reactions at the Typhim Vi and at the Menactra
 8 injection sites were reported as Grade 1 and resolved within 3 days post-vaccination. The most

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1 common systemic reactions were headache (41% when Menactra and Typhim Vi were given
2 concomitantly; 42% when Typhim Vi was given with Placebo, and 33% when Menactra vaccine
3 was given alone one month after Typhim Vi vaccination) and fatigue (38% when Menactra
4 vaccine and Typhim Vi were given concomitantly; 35% when Typhim Vi was given with
5 Placebo, and 27% when Menactra vaccine was given alone one month after Typhim Vi
6 vaccination). Fever $\geq 40.0^{\circ}\text{C}$ and seizures were not reported.

7

8 **DATA FROM WORLDWIDE POST-MARKETING EXPERIENCE**

9 In addition to reports in clinical trials, worldwide voluntary adverse events reports received since
10 market introduction of Typhim Vi vaccine are listed below. This list includes serious events
11 and/or events which were included based on severity, frequency of reporting or a plausible causal
12 connection to Typhim Vi vaccine. Because these events were reported voluntarily from a
13 population of uncertain size, it is not possible to reliably estimate their frequency or establish a
14 causal relationship to vaccination.

15

- 16 • Gastrointestinal disorders
17 Nausea, vomiting, diarrhea, abdominal pain
- 18 • General disorders and administration site condition
19 Injection site pain, inflammation, induration, and erythema; lymphadenopathy, fever,
20 asthenia, malaise, flu-like episode
- 21 • Immune system disorders
22 Anaphylaxis, allergic-type reactions such as pruritus, rash, urticaria, angioedema,
23 difficulty breathing, hypotension; serum sickness

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- 1 • Musculoskeletal and connective tissue disorders
- 2 Myalgia, arthralgia, cervical pain
- 3 • Nervous system disorders
- 4 Syncope with and without convulsions, headache, loss of consciousness, tremor
- 5 • Respiratory system disorders
- 6 Asthma

7

8 Additional Adverse Events:

9 Post-marketing reports of glomerulonephritis, neutropenia, bilateral retinitis, and polyarthritis
10 have been reported in patients who had also received other vaccines; however, a causal
11 relationship has not been established.

12

13 **REPORTING OF ADVERSE EVENTS**

14 Reporting by parents and patients of all adverse events occurring after vaccine administration
15 should be encouraged. Adverse events following immunization with vaccine should be reported
16 by the health-care provider to the US Department of Health and Human Services (DHHS)
17 Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about
18 reporting requirements or completion of the form can be obtained from VAERS through a toll-
19 free number 1-800-822-7967 or visit the VAERS website at <http://www.vaers.org>. (17)

20

21 **Health-care providers also should report these events to the Pharmacovigilance**
22 **Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370, or call 1-800-822-**
23 **2463.**

1

2 **DOSAGE AND ADMINISTRATION**

3 Parenteral drug products should be inspected visually for particulate matter and discoloration
4 prior to administration, whenever solution and container permit. The syringe or vial and its
5 packaging should also be inspected prior to use for evidence of leakage, premature activation of
6 the plunger, or a faulty tip seal. If any of these conditions exists, the vaccine should not be
7 administered.

8

9 For intramuscular use only. Do NOT inject intravenously.

10

11 The immunizing dose for adults and children is a single injection of 0.5 mL. The dose for adults is
12 typically given intramuscularly in the deltoid, and the dose for children is given IM either in the
13 deltoid or the anterolateral thigh. The vaccine should not be injected into the gluteal area or areas
14 where there may be a nerve trunk.

15

16 A reimmunizing dose is 0.5 mL. Reimmunization consisting of a single dose for US travelers
17 every two years under conditions of repeated or continued exposure to the *S typhi* organism is
18 recommended at this time. (14)

19

20 The syringe is intended for single use only, must not be reused, and must be disposed of properly
21 and promptly following its use.

22

1 The skin at the site of injection first should be cleansed and disinfected. Tear off upper seal of vial
2 cap. Cleanse top of rubber stopper of the vial with a suitable antiseptic and wipe away all excess
3 antiseptic before withdrawing vaccine.

4

5 **HOW SUPPLIED**

6 Syringe, without needle, 0.5 mL, NDC 49281-790-88. Packaged as NDC 49281-790-51.

7 Vial, 20 Dose, NDC 49281-790-38. Packaged as NDC 49281-790-20.

8

9 **STORAGE**

10 Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE.

11

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Confidential/Proprietary Information

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13

14

1 Product Information as of March 2014.

2

3 Manufactured by:

4 **Sanofi Pasteur SA**

5 Lyon, France

6 US Govt License #1724

7

8 Distributed by:

9 **Sanofi Pasteur Inc.**

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