

Product Monograph

TYPHERIX[®]

Salmonella typhi Vi Capsular Polysaccharide Vaccine

Liquid for injection

Active Immunizing Agent

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Clinical Pharmacology

Typhoid fever is an acute generalized infection caused by *Salmonella typhi*, an organism for which humans are the only reservoir. The disease affects the reticuloendothelial system, intestinal lymphoid tissue and gall bladder.⁽¹⁾

The course of typhoid fever may be insidious, with fever that increases in stepwise fashion to reach 39 - 40°C, malaise, anorexia, myalgia, headache and abdominal discomfort. Without appropriate anti-microbial therapy, the fever remains for approximately 10-14 days. The most frequent serious complications, intestinal perforation and haemorrhage, occur in 0.5 to 1.0% of the infected population.⁽¹⁾

Typhoid fever is still a common disease and although its incidence is decreasing globally, it is still increasing in Asia, Africa and Latin America where more than 500 cases/100,000 people/year occur and where mortality is significant. In these developing countries, satisfactory control of drinking water, food and sewage disposal has not yet been achieved. Infection is transmitted when susceptible hosts ingest fecally contaminated food or water; small numbers of organisms are ingested and many subclinical and mild infections occur for each fullblown clinical case of the disease.⁽²⁾

In endemic areas, the majority of clinical infections occur in 3 to 19 year old children, the incidence decreases in adults from the age of 35 years. In contrast, common-source food outbreaks occur in more developed countries when chronic carriers contaminate food following a breakdown in personal and food hygiene; large numbers of organisms are present, attack rates are high and relatively few subclinical cases follow.⁽²⁾

Although the incidence of typhoid fever is declining steadily in Canada, about 90 cases are still reported annually. Only a small number of these infections occur in Canada with the vast majority occurring abroad. The decline in incidence of the disease has been primarily due to improved living conditions and to water and sewage treatment. Vaccine is not believed to have played a significant role. For travelers to areas where sanitation is likely to be poor, immunization is not a substitute for careful selection and handling of food and water.⁽³⁾

Clinical trials have been carried out in over 1,570 subjects, to compare seropositivity (seroconversion is defined as an increase in anti-Vi antibody titres from <150 EL.U/mL pre vaccination to ≥150 EL.U/mL post vaccination) and geometric mean titres (GMT's) in subjects receiving either TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) or TYPHIM Vi[®], (Sanofi Pasteur).

Two weeks after vaccination, seropositivity rates were at a maximum of 96.5% and 96.8% and GMTs were at 1,554 and 1,656 EL.U/mL in TYPHERIX[®] and TYPHIM Vi[®], (Sanofi Pasteur) respectively.

Two years following vaccination, seropositivity rates were 61.4% and 45.9%, and GMT's were 290 and 235 EL.U/mL in TYPHERIX[®] and TYPHIM Vi[®], (Sanofi Pasteur), respectively.

An age related trend could be observed in GMT's: the youngest age-group had a mean GMT of 3,597 EL.U/mL compared with a mean of 1,966 EL.U/mL in adolescents. One month following vaccination, similar seroconversion rate was observed with 99.3% in children and 98.9% in adolescents. TYPHERIX[®] proved to be immunogenic in both groups, with higher GMT's in children. Antibodies persisted in over 94% of those subjects available to be tested at month 6.

Immunity persists for at least 3 years.⁽⁴⁾

Indications and Clinical Use

TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) is indicated for active immunization against typhoid fever in persons two years of age and older. One dose administered intramuscularly ensures protection for at least 3 years.⁽⁴⁾ The vaccine must be given at least 2 weeks prior to travel to endemic areas.

The Canadian Immunization Guide (CIG)⁽³⁾ recommends vaccination for:

1. Travelers who will have prolonged exposure to potentially contaminated food and water, especially those traveling to or working in small cities and villages, or to rural areas in countries with a high incidence of disease. Vaccination is not routinely recommended for short-term travel to resort hotels in such countries.
2. Persons with on-going household or intimate exposure to an *S. typhi* carrier.
3. Laboratory workers who frequently handle cultures of *S. typhi*.

Contraindications

TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) should not be administered to subjects with known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration.

As with other vaccines, the administration of TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) should be postponed in subjects suffering from acute severe febrile illness.

Warnings

The vaccine 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 emphasized for all persons at risk of typhoid fever.

TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) should under no circumstances be administered intravascularly.

Precautions

General

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

TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) should be administered with caution to subjects with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular administration to these subjects: following injection, firm pressure should be applied to the site (without rubbing) for at least two minutes.

Use in Children

TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) has not been evaluated in children under 2 years of age. Nevertheless, it is known that children under this age may show a suboptimal response to polysaccharide antigen vaccines. The decision to use the vaccine in this age group should be based upon the risk of exposure to disease.

Use in Pregnancy

The effect of TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) on fetal development has not been assessed. However, as with other purified polysaccharide vaccines, no effect is expected.

TYPHERIX[®] should only be used during pregnancy when there is a high risk of infection.

Nursing Mothers

The effect on breast fed infants of the administration of TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) to their mothers has not been evaluated in clinical studies. TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) should therefore only be used in breast-feeding women, when there is a high risk of infection.

Drug Interaction

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate response may not be achieved.

In clinical studies in adults, TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) has been administered simultaneously with HAVRIX[®] 1440, GlaxoSmithKline Biologicals' inactivated hepatitis A vaccine. There was no adverse effect on either the reactogenicity or immunogenicity of the vaccines when they were administered simultaneously.

The concomitant administration of TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) and vaccines other than HAVRIX[®] 1440 has not specifically been studied.

Adverse Reactions

The reactogenicity of TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) was determined by systematic recording of local and general reactions to the vaccine. General symptoms occurred more frequently in adolescents and older children than in the adult and younger populations; it is not clear why this phenomenon was observed, but it can be said that the vast majority of symptoms reported were mild and transient in nature. The most frequent local symptom reported was soreness at the injection site, and headache and fever were the most frequent general symptoms.

In clinical studies, in the majority of instances, redness, pain and swelling were usually reported only during the first 48 hours following immunization. The most common reaction, soreness, has been reported in approximately 7% of vaccinees.

In clinical studies, systemic reactions were also transient; the incidence of the most frequently reported symptoms, fever, headache, general aches, malaise, nausea and itching did not exceed 9%.

Anaphylaxis, allergic reactions, including anaphylactoid reactions and urticaria have been reported very rarely with TYPHERIX[®].

Table 1: Incidence of Solicited Local Symptoms in Healthy Adults

Symptom (N=551)		n	%
Soreness	All	52	9.4
	graded "3"	2	0.4
Redness	All	30	5.4
	>30 mm	1	0.2
Swelling	All	10	1.8
	>30 mm	0	-

Notes:

N = total number of symptom sheets returned

n = number of symptom sheets with a report of a symptom

graded "3": severe: adverse experience which prevents normal everyday activities

Table 2: Incidence of Solicited General Symptoms in Healthy Adults

Symptom (N=400)		n	%
Fever	All	6	1.5
Headache	All	31	7.8
	graded "3"	2	0.5
General aches	All	5	1.3
Malaise	All	16	4.0
Nausea	All	20	5.0
Itching	All	7	1.8
	graded "3"	1	0.3

Notes:

No general aches, malaise or nausea graded "3" or temperature >39°C reported

graded "3": severe: adverse experience which prevents normal everyday activities

**Table 3: Frequency of Solicited Symptoms in Adolescents and Children
(Studies 003, 005, 006)**

		005 (11-18 yrs) N=99		003 (5-15 yrs) N=199		006 (2-5 yrs) N=170	
		n	%	n	%	n	%
Local symptoms							
Soreness	All	16	16.2	1	0.5	0	-
Redness	All	1	1.0	1	0.5	9	5.3
Swelling	All	1	1.0	7	3.5	0	-
General symptoms							
Fever	All	8	8.1	63	31.7	5	2.9
	> 39°C	2	2.0	4	2.0	0	-
Headache	All	19	19.2	28	14.1	0	-
General aches	All	13	13.1	6	3.0	1	0.6
Malaise	All	4	4.0	0	-	0	-
Nausea	All	3	3.0	7	3.5	0	-
Itching	All	8	8.1	0	-	0	-

Notes:

N = total number of symptom sheets returned

n = number of symptom sheets with a report of a symptom

graded "3": severe: adverse experience which prevents normal everyday activities

Dosage and Administration

Dosage

A. Primary Immunization

A single dose of 0.5 mL containing 25 µg of the Vi polysaccharide of *Salmonella typhi* is recommended.

For adults 19 years and older TYPHERIX® (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) can be co-administered with HAVRIX® 1440 in opposite arms.

For other injectable vaccines, different syringes and different injection sites must be used.

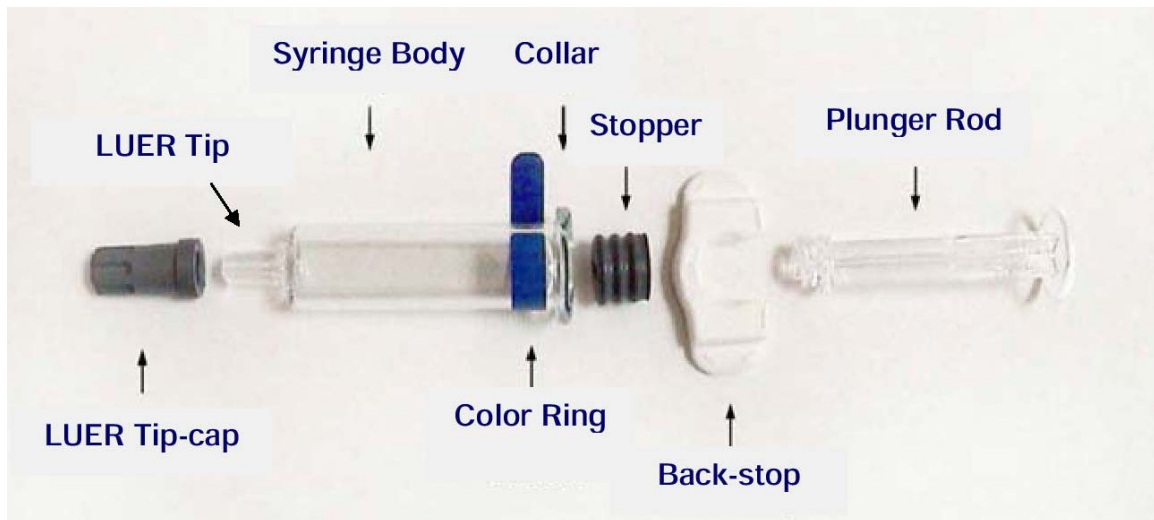
B. **Booster Dose**

For individuals who remain at risk, or who may be re-exposed to risk of typhoid fever, it is recommended that they be revaccinated using a single dose of vaccine every 3 years.

Method of Administration

TYPHERIX[®] (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) is for **intramuscular** injection. Vaccines should be inspected for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the vaccine.

Do not remove the white back-stop from the syringe. Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger clockwise until slight resistance is felt. **Do not** over tighten. Remove syringe LUER Tip-cap and needle cap. Attach needle by pressing and twisting in a clockwise rotation until secured to the syringe.



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TYPHERIX® (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) should under no circumstances be administered intravascularly.

Pharmaceutical Information

Composition

TYPHERIX® (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) is a clear colourless liquid containing the cell surface Vi polysaccharide extracted from *Salmonella typhi* Ty2 strain.

The amount of Vi capsular polysaccharide (25 µg) complies with the European Pharmacopoeia and WHO recommendations for a Vi polysaccharide typhoid vaccine. The excipients present in the finished product are sodium chloride, sodium phosphate dihydrate, disodium phosphate dihydrate, phenol and water for injection.

Each 0.5 mL dose of vaccine contains 25 µg of the Vi polysaccharide of *Salmonella typhi*.

Stability and Storage Recommendations

The expiry date of the vaccine is indicated on the label and packaging.

Store at +2 to +8°C. Protect from light.

DO NOT FREEZE; discard if vaccine has been frozen.

Availability of Dosage Forms

TYPHERIX® (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) is available as a single dose of 0.5 mL containing 25 µg of the Vi polysaccharide of *Salmonella typhi*.

Package sizes: Single dose prefilled syringe in packages of 1, 10, 50, and 100's.

References

1. Levine MM. Typhoid Fever Vaccines. In Vaccines. Ed Plotkin SA, Orenstein WA. WB Saunders Company. 1999;781-814
2. Recommendations of the Advisory Committee on Immunization Practices. MMWR 1990; 39 (RR-10):1-5 (updated: 1994)
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4. Klugman KP, Koornhof HJ, Robbins JB, Le Cam NN. Immunogenicity, efficacy and serological correlate of protection of Salmonella typhi Vi capsular polysaccharide vaccine three years after immunization. Vaccine. 1996;14(5):435-438.