PRODUCT MONOGRAPH

TYPHERIX®

Salmonella typhi Vi Capsular Polysaccharide Vaccine

Liquid for injection

Active Immunizing Agent

GlaxoSmithKline Inc.
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular Injection	Liquid for injection /25 micrograms Vi capsular polysaccharide of *Salmonella typhi* per 0.5 mL dose	Sodium phosphate dihydrate Disodium phosphate dihydrate Sodium chloride Phenol Water for injection *For a complete listing see Dosage Forms, Composition and Packaging section.*

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. The vaccine must be given at least 2 weeks prior to travel to endemic areas.

The Canadian Immunization Guide (CIG) 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® 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. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

As with other vaccines, the administration of TYPHERIX® should be postponed in subjects suffering from acute severe febrile illness.

WARNINGS AND PRECAUTIONS

General

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® should under no circumstances be administered intravascularly.

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.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

TYPHERIX® 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.

Special Populations

Pregnant Women: Adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

Nursing Women: Adequate human data on use during lactation and adequate animal reproduction studies are not available.

Pediatrics: TYPHERIX® 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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The reactogenicity of TYPHERIX® 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 vaccines.

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

DRUG INTERACTIONS

Drug-Drug Interactions

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® 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® and vaccines other than HAVRIX® 1440 has not specifically been studied.

DOSAGE AND ADMINISTRATION

Recommended Dose

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® can be co-administered with HAVRIX® 1440 in opposite arms.

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

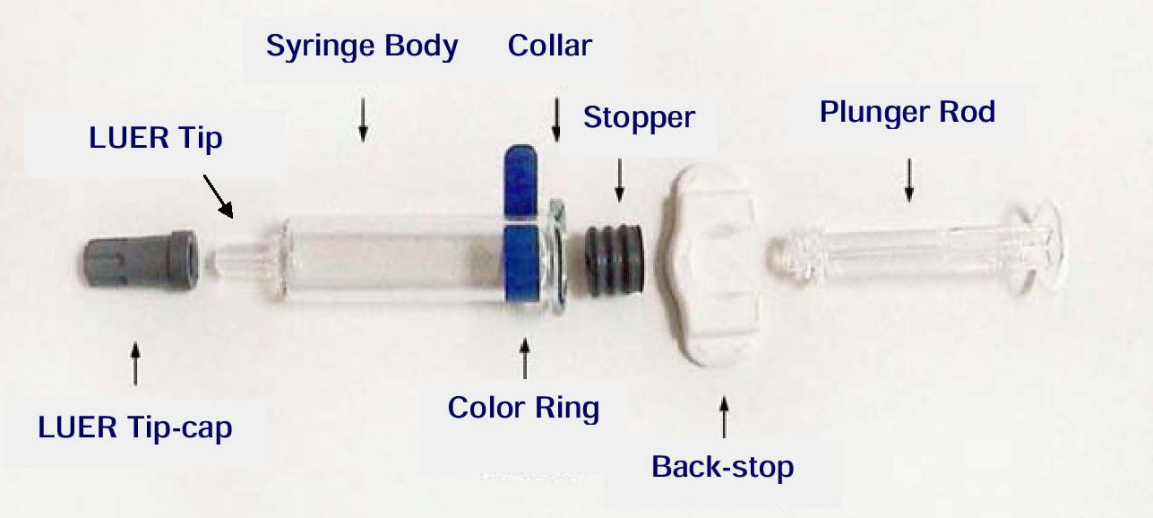
Booster Dose

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.

Administration

TYPHERIX® 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.



TYPHERIX® 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.

TYPHERIX® should under no circumstances be administered intravascularly.

OVERDOSAGE

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

ACTION AND 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 to 40°C, malaise, anorexia, myalgia, headache and abdominal discomfort. Without appropriate anti-microbial therapy, the fever remains for approximately 10 to14 days. The most frequent serious complications, intestinal perforation and haemorrhage, occur in 0.5 to 1.0% of the infected population.

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.

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.

Although the incidence of typhoid fever is declining steadily in Canada, about 70cases have been reported annually over the past 5 years. 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.

STORAGE AND STABILITY

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

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

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

Composition

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.*

Packaging

Package sizes:

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: *Salmonella typhi Vi polysaccharide vaccine*

CLINICAL TRIALS

Study results

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.

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).

3. National Advisory Committee on Immunization. Canadian Immunization Guide. Ministry of Supply and Services. Government of Canada. 7th Edition 2006.

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.

PART III: CONSUMER INFORMATION

TYPHERIX®

Salmonella typhi Vi Capsular Polysaccharide Vaccine

This leaflet is part III of a three-part "Product Monograph" for TYPHERIX® and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TYPHERIX®. Contact your health professional if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:
TYPHERIX® is a vaccine that may be given to persons 2 years of age and older to help prevent against typhoid fever, an infectious illness caused by a type of bacteria called *Salmonella typhi*.

What it does:
TYPHERIX® contains a small part of the bacterium which causes typhoid fever. This is not infectious and cannot make you ill.

When you are given the vaccine it will trigger the body's immune system to prepare itself to protect against typhoid fever in the future.

Typhoid fever is an infectious illness caused by a bacterium, *Salmonella typhi*. It is caused and spread by eating or drinking contaminated food or water. Since the bacterium is present in the bowel movement (motion), the infection can occur in any country, but it more commonly occurs in places or countries with poor personal or public hygiene.

The main signs of the illness include headache, pains in the stomach, constipation or diarrhoea and a fever that may last for one or two weeks.

When it should not be used:
Please see WARNINGS AND PRECAUTIONS section.

What the medicinal ingredient is:
Each 0.5 mL dose contains 25 micrograms of the Vi polysaccharide antigen, a part of the *Salmonella typhi* (Ty2 strain) bacterium that causes typhoid fever.

What the important nonmedicinal ingredients are:
TYPHERIX® contains the following non-medicinal ingredients: sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, phenol and water for injections.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
TYPHERIX® is presented in a single dose prefilled syringe.

WARNINGS AND PRECAUTIONS

TYPHERIX® should not be given if you have previously had had any allergic reaction to TYPHERIX®, or any ingredient contained in TYPHERIX®. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

TYPHERIX® will only prevent disease caused by the bacterium *Salmonella typhi* and not against salmonella bacteria that can cause food poisoning or gastroenteritis.

BEFORE you use TYPHERIX® talk to your health professional if:

- you or your child have/has a severe infection with a high temperature. In these cases, the vaccination will be postponed until recovery. A minor infection such as a cold should not be a problem, but talk to your health professional first.
- you or your child have/has a bleeding problem or bruise(s) easily.
- you or your child have/has a weakened immune system, for example due to HIV infection or due to medicines that suppress the immune system. You or your child may not get the full benefit from TYPHERIX®.

Fainting can occur following, or even before, any needle injection, therefore tell your health professional if you/your child fainted with a previous injection.

INTERACTIONS WITH THIS VACCINE

Please tell your health professional if you/your child are/is taking or have/has recently taken any other medicines, including medicines obtained without a prescription or have/has recently received any other vaccine.

TYPHERIX®™ may not work as well if you/your child are/is taking medicines that reduce the effectiveness of your/your child's immune system to fight infection

TYPHERIX® can be given at the same time as some other vaccines. Your health professional will ensure that the vaccines are injected separately and into different parts of the body.

PROPER USE OF THIS VACCINE

Usual dose:
Your health professional will give TYPHERIX® as an injection into the muscle. TYPHERIX® is given as one injection of 0.5 mL at least 2 weeks before being exposed to typhoid fever.

If you remain at risk of catching typhoid fever, your health professional may recommend a second dose of TYPHERIX® within 3 years of the first dose.

Overdose:

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Allergic reactions (these may occur with up to 1 in 10,000 doses of the vaccine)

If you have an allergic reaction, see your health professional straight away. The signs may include:

- your face swelling
- low blood pressure
- difficulty breathing your skin going blue
- loss of consciousness.

The signs usually start very soon after the injection has been given to you. See a health professional straight away if they happen after leaving the clinic.

Other side effects include:
Common (these may occur with up to 1 in 10 doses of the vaccine):

- pain, redness and swelling at the injection site
- a high temperature (fever)
- headache
- general aches and pains
- feeling generally unwell
- feeling sick
- itching

Very Rare (these may occur with up to 1 in 10,000 doses of the vaccine)

- severe rashes (urticaria)

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your health professional.

This is not a complete list of side effects. For any unexpected effects while taking TYPHERIX®, contact your health professional.

HOW TO STORE IT

Keep out of reach and sight of children. Store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original package in order to protect from light.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

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.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

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
At the following website:
http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

By regular mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario
K1A 0K9 Address Locator 6502A

NOTE: Should you require information related to the management of the side effect, 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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.gsk.ca
or by contacting the sponsor, GlaxoSmithKline Inc.
7333Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

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