PRODUCT MONOGRAPH

Vivotif®

TYPHOID VACCINE LIVE ORAL ATTENUATED TY21A

ACTIVE IMMUNIZING AGENT

A package of Vivotif® contains a single foil blister with 4 enteric-coated capsules (each containing one dose of lyophilized bacteria) for oral administration.

Pharmaceutical Standard: prescribed

Therapeutic Classification: J07AP01

Manufactured by:
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Vivotif®

TYPHOID VACCINE LIVE ORAL ATTENUATED TY21A

ACTIVE IMMUNIZING AGENT

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Nonmedicinal Ingredients
Oral	Enteric coated capsule: Viable *S. typhi* Ty21a $2.0 – 10.0 \times 10^9$ colony-forming units	Amino acid mixture, ascorbic acid, lactose, magnesium stearate, sucrose. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Vivotif® (Typhoid vaccine live oral attenuated Ty21a) is indicated for:

immunization of adults and children against disease caused by *Salmonella typhi* (new nomenclature: *Salmonella enterica* subspecies *enterica* serovar Typhi).

Results from clinical studies indicate that adults and children 5 years and older may be protected against typhoid fever following the oral ingestion of 4 doses of Vivotif® (enteric-coated capsules).

Immunization (ingestion of all 4 capsules) should be completed at least 1 week prior to exposure to *S. typhi* (see DOSAGE AND ADMINISTRATION).

Routine typhoid vaccination is not recommended in Canada but immunization should be considered in the following situations:[1, 2]

1) travel in endemic areas for extended periods, or off the usual tourist tracks;
2) on-going household or intimate exposure to a typhoid carrier;
3) laboratory workers who frequently handle cultures of *S. typhi*.

Not all recipients of Vivotif® will be fully protected against typhoid fever. Travellers should take all necessary precautions to avoid contact with or ingestion of potentially contaminated food or water.

There is no evidence to support the use of typhoid vaccine to control common source outbreaks, disease following natural disasters or in persons attending rural summer camps.

Vivotif® will not afford protection against enteric organisms other than *S. typhi*.

There are no studies reported using Vivotif® as a booster for persons previously vaccinated with the parenteral vaccine.

An optimal booster dose has not yet been established. However, it is recommended that a booster dose consisting of 4 capsules taken on alternate days be given every 7 years under

conditions of repeated or continued exposure to typhoid fever (see DOSAGE AND ADMINISTRATION).

Typhoid fever continues to be an important disease in many parts of the world. Travellers entering such areas are at risk of contracting typhoid fever following the ingestion of contaminated food or water.

Geriatrics:
No data available.

Pediatrics (< *5* years of age):
The efficacy of Vivotif® (enteric-coated capsules) has not been established in children under 5 years of age. The capsule formulation is therefore not recommended for use in children under 5 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to any component of the vaccine or the enteric-coated capsule. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Safety of the vaccine has not been demonstrated in persons deficient in their ability to mount a humoral or cell-mediated immune response due to either a congenital or acquired immunodeficient state, including treatment with immunosuppressive or antimitotic drugs. The vaccine should not be administered to these persons regardless of benefits.

WARNINGS AND PRECAUTIONS

General
The vaccine should not be administered to persons during an acute febrile illness.

Carcinogenesis and Mutagenesis
No data available.

Cardiovascular
No data available.

Dependence/Tolerance
No data available.

Ear/Nose/Throat
No data available.

Endocrine and Metabolism
No data available.

Gastrointestinal
The vaccine should not be administered to persons during an acute gastrointestinal illness.

Genitourinary
No data available.

Hematologic
No data available.

Hepatic/Biliary/Pancreatic
No data available.

Immune
No data available.

Neurologic
No data available.

Ophthalmologic
No data available.

Peri-Operative Considerations
No data available.

Psychiatric
No data available.

Renal
No data available.

Respiratory
No data available.

Sensitivity/Resistance
No data available.

Sexual Function/Reproduction
No data available.

Skin
No data available.

Special Populations
No data available.

Pregnant Women:
Animal reproduction studies have not been conducted with Vivotif®. It is not known whether Vivotif® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Vivotif® should be given to a pregnant woman only if clearly needed.

Nursing Women:
There are no data to support the use of this product in nursing mothers. It is not known if Vivotif® is excreted in human milk.

Pediatrics (< 5 years of age):

The safety of Vivotif® (enteric-coated capsules) has not been established in children under 5 years of age. The capsule formulation is therefore not recommended for use in children under 5 years of age.

Geriatrics:
No data available.

Monitoring and Laboratory Tests
Not applicable

ADVERSE REACTIONS

Adverse Drug Reaction Overview
No serious adverse systemic reactions were reported in clinical trials. Several lots of Vivotif® (Typhoid Vaccine Live Oral Attenuated Ty 21a) have been evaluated in several field trials both in adults and in school-aged children. There were no statistically significant differences for solicited adverse events, i.e. abdominal pain, diarrhea, vomiting, fever, except the higher incidence of nausea and skin rash in vaccine recipients versus placebo group.[3] Post-marketing surveillance for over 20 years has found that side-effects are in general infrequent and mild.[4] Reported adverse reactions include nausea, abdominal pain, vomiting, diarrhea, fever, headache, skin rash or urticaria in the trunk and/or extremities.

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*.

Several lots of Vivotif® (Typhoid vaccine live oral attenuated Ty21a) have been evaluated in field trials both in children and adults. In an Indonesian field trial, Vivotif® was compared to placebo for its potential to cause side-effects.[5] There were no statistically significant differences for solicited adverse events, i.e. abdominal pain, diarrhea, vomiting, fever, nausea, except the higher incidence of skin rash and nausea in vaccine recipients versus placebo group. In contrast to the side effects in the Indonesian trial, solicited adverse events did not occur at a statistically higher frequency among Chilean school children[6] (enteric-coated capsules), 2 - 6 year old Thai children[7, 8] (sachet formulation) or adult Europeans[4] who received the vaccine as compared to a placebo group.

The following adverse reactions have been reported in clinical studies:

Gastrointestinal disorders
Frequent (>1/100, <1/10)
Abdominal pain
Nausea
Diarrhoea
Vomiting

General disorders and administration site conditions
Frequent (>1/100, <1/10)
Fever
Nervous system disorders
Frequent (>1/100, <1/10)
Headache
Skin and subcutaneous disorders
Frequent (>1/100, <1/10)
Rash

These reported symptoms disappeared spontaneously within a few days. No serious adverse systemic reactions were reported.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
No data available

Abnormal Hematologic and Clinical Chemistry Findings
No data available

Post-Market Adverse Drug Reactions
Experience from postmarketing surveillance has confirmed that adverse reactions are rare: Over 122 million capsules of Vivotif® were sold between 1991 and 2004, which corresponds to about 40 million vaccinations. During this period, 3.6 adverse reactions were reported per 100'000 immunisations. The following adverse reactions were reported spontaneously:

Gastrointestinal disorders
Abdominal pain
Diarrhoea
Nausea
Vomiting

General disorders and administration site conditions
Fever

Nervous system disorders
Headache

Skin and subcutaneous disorders
Skin reactions such as dermatitis, exanthema, pruritus, and urticaria

The following symptoms have been reported in isolated cases:

General disorders and administration site conditions
Asthenia, malaise, tiredness, cold, shivering

Nervous system disorders
Paresthesia, dizziness

Musculoskeletal, connective tissue and bone disorders
Arthralgia, myalgia

The following symptoms have been reported in very rare cases:

Immune system disorders
Allergy, anaphylactic reaction

DRUG INTERACTIONS

Overview

Antibiotics
Because the growth of vaccine organisms may be inhibited by the concomitant intake of sulfonamides or antibiotics, vaccination should be started at least three days after treatment with these agents. Accordingly, therapy with sulfonamides or antibiotics should preferably be started at least three days after the last dose of Vivotif®

Alcohol
Alcoholic beverages should not be consumed one hour before or two hours after taking Vivotif®

Drug-Drug Interactions

Several anti-malaria drugs, such as mefloquine, chloroquine and proguanil possess anti-bacterial activity which may interfere with the immunogenicity of Vivotif® (Typhoid vaccine live oral attenuated Ty21a).[9,10] However, it was shown that the administration of chloroqine, mefloquine and the combination product pyrimethamine/sulphadoxine did not influence the immune response to Vivotif®.[11] Furthermore, the effect of anti-malaria drugs on the humoral anti-*S. typhi* immune response was determined: Healthy adult subjects were given mefloquine (250 mg at weekly intervals; N = 30), chloroquine (500 mg at weekly intervals; N = 30) or proguanil (200 mg daily; N = 30) together with the *S. typhi* Ty21a vaccine strain.[12] Concomitant treatment with mefloquine or chloroquine did not result in a significant ($p > 0.05$) reduction in the serum anti-*S. typhi* immune response compared to subjects receiving vaccine only (N = 45). The simultaneous administration of the single agent proguanil did effect a significant ($p = 0.01$) decrease in the immune response rate. However, although proguanil is known to have antibacterial activity, it was shown, in a study involving 330 subjects between 4 to 16 years of age[13], that the combination product atovaquone/proguanil (62.5-187.5 mg/day atovaquone depending on the body weight and 25-75 mg/day proguanil depending on the body weight) did not affect the vaccinees' immune response to Vivotif® ($p > 0.05$), when using the commercialised combination product (Malarone®). This finding indicates that the combination product atovaquone/proguanil can be administered together with Vivotif®.

When planning malaria prophylaxis as well as typhoid prophylaxis, the fixed combinations of atovaquone and proguanil hydrochloride or pyrimethamine and sulfadoxine can be given concomitantly with Vivotif®. Likewise, the administration of Vivotif® and mefloquine or chloroquine can be given concomitantly.

When using any other antimalarial, immunization with Vivotif® should precede antimalarial prophylaxis. The interval between the last Vivotif® dose and the beginning of malaria prophylaxis should generally be three days.

The concomitant administration of oral polio vaccine or yellow fever vaccine did not suppress the immune response elicited by *S. typhi* Ty21a vaccine strain.[12] There is no reason to believe that simultaneous administration of parenteral vaccines or immunoglobulins with Vivotif® will decrease vaccine efficacy.

Drug-Food Interactions
Interaction with specific foods have not been established.

Drug-Herb Interactions
Interaction with herbal products have not been established.

Drug-Laboratory Interactions
Interaction with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Not applicable.

Recommended Dose and Dosage Adjustment
The vaccine is to be taken approximately one hour before, or two hours after a meal as described below. A complete immunization schedule is the ingestion of 4 enteric-coated capsules taken on alternate days; e.g. one capsule on days 1, 3, 5 and 7. Unless a complete immunization schedule is followed, an optimum immune response may not be achieved. Not all recipients of Vivotif® (Typhoid vaccine live oral attenuated Ty21a) will be fully protected against typhoid fever. Travellers should take all necessary precautions to avoid contact with or ingestion of potentially contaminated food or water.

Administration of Vivotif® should be as follows. The blister containing the vaccine capsules should be inspected to ensure that the foil seal and the capsules are intact. Capsules should be taken with at least 4 oz of cool or lukewarm water [temperature not to exceed body temperature; e.g., 98.6 °F (37 °C)] on the recommended every-other-day dosing schedule, e.g., one capsule days 1, 3, 5 and 7. The vaccine capsules should not be chewed but swallowed as soon as possible after placing in the mouth.

Booster Use: The optimum booster schedule for Vivotif® has not been determined. Protective efficacy has been shown to persist for at least 7 years. However, there is no experience with Vivotif® as a booster in persons previously immunized with parenteral typhoid vaccine. Despite these limitations, it is recommended that a booster dose consisting of 4 enteric coated capsules taken as one capsule on alternate days be given every 7 years under conditions of repeated or continued exposure to typhoid fever.

Vivotif® (one capsule) is to be swallowed approximately 1 hour before, or two hours after meals.

Missed Dose

The protection conferred by Vivotif® is based on each dose of Ty21a vaccine strain having optimum time stimulating the immune system before lysing. Once absorbed, each dose of the Ty21a strain replicates 3-5 times and then lyses over an approximate 48 hour period. Hence the doses are spaced every other day to achieve the optimum stimulation to the immune system over the 7 day vaccination period.

The 7 days period is based on clinical data showing that the population of antibody secreting cells peaks between 7 to 10 days after the first dose. This suggests that it is of primary importance to finish the course within 7 days.
Any variation from the recommended schedule (i.e. every-other-day over a 7 days) would be off-label use. In other words, a 72 hours gap between two doses instead of 48 hours, or the full course taken over 8 days instead of 7 is unlikely to have a marked effect on efficacy because of the peaking of the antibody secreting cells within 7 to 10 days. However, as there is no clinical data on such schedules it is not possible to be specific about the effect of these schedules on the % protection conferred.

OVERDOSAGE

Five to eight doses of the vaccine strain Ty21a containing between 3-10 x 10^{10} viable vaccine organisms were administered to 155 healthy adult males. This dosage was, at a minimum, 3-fold higher than the currently recommended dose. No significant reactions, e.g. vomiting, acute abdominal distress or fever were observed. At the recommended dosage, the *S. typhi* Ty21a vaccine strain is not excreted in the feces. However, clinical studies in volunteers have shown that overdosage can increase the possibility of shedding *S. typhi* Ty21a in low amounts in the feces. After 3 days, only one of 155 test subjects had *S. typhi* Ty21a vaccine strain positive feces.[14]

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Vivotif® (Typhoid vaccine live oral attenuated Ty21a) is a live attenuated vaccine for oral administration. The vaccine contains the attenuated strain *Salmonella typhi* Ty21a.

Salmonella typhi (new nomenclature: *Salmonella enterica* subspecies *enterica* serovar Typhi) is the etiological agent of typhoid fever, an acute, febrile enteric disease. This vaccine will not afford protection against species of *Salmonella* other than *Salmonella typhi* or against any other bacteria that cause enteric disease.

Upon ingestion, virulent strains of *S. typhi* are able to pass through the stomach acid barrier, colonize the intestinal tract, penetrate the lumen and enter the lymphatic system and blood stream, thereby causing disease. The risk of severe illness is increased in the absence of gastric acid, e.g. prior gastrectomy, antacid therapy, H_2 antagonist therapy, or in immunocompromised individuals. One possible mechanism by which disease may be prevented is by evoking a local immune response in the intestinal tract. Such local immunity may be induced by oral ingestion of a live attenuated strain of *S. typhi* which causes an aborted infection.

The ability of *S. typhi* to cause disease and to induce a protective immune response is dependent upon the bacteria possessing a complete lipopolysaccharide.[15,16] The *S. typhi*

Ty21a vaccine strain, derived by chemical mutagenesis, is entirely deficient in activity of the gal E gene product, which restricts its ability to produce complete lipopolysaccharide. In addition, Ty21a has several nutritional auxotrophies, has approximately half the growth rate of the parent strain Ty2, does not produce H_2S, and lacks the Vi antigen (capsular acidic polysaccharide present on almost all virulent *S. typhi* strains). Ty21a, grown in the presence of low concentrations of galactose, is immunogenic, suggesting that the uptake of galactose by Ty21a enables production of lipopolysaccharide, leading to immunogenicity. It has been presumed that an oversupply of galactose results in accumulation of toxic metabolites within the bacterial cells leading to bacterial lysis. Attenuation and safety of Ty21a have been presumed to be due to the combination of gal E mutation and the lack of Vi antigen. However, an analogous mutant (Vi negative, gal E deletion mutant) of *S. typhi* constructed by recombinant DNA techniques has been shown to be virulent.[17] In addition, galactose induced lysis of Ty21a is inhibited *in vitro* in the presence of glucose. Therefore, the combination of gal E and Vi mutations does not account for the safety of Ty21a or for the failure to recover vaccine organisms from people ingesting the usual dose. Ty21a is attenuated by an incompletely understood mechanism.

Pharmacodynamics
Not applicable for vaccines

Pharmacokinetics
Not applicable

STORAGE AND STABILITY

Vivotif® (Typhoid vaccine live oral attenuated Ty21a) is not stable when exposed to room temperatures. Vivotif® should be shipped and stored at refrigerated temperatures between 35.6 °F and 46.4 °F (2 °C and 8 °C). Vaccine capsules should be stored in the refrigerator between doses. The vaccine may be left out of refrigeration during a reasonable transit time home from the clinic. If the capsules are left outside of refrigeration at room temperature 77 °F (25 °C) for up to 12 hours on a one-time only occasion, the product quality will not be affected, and the capsules can still be taken. Each blister of vaccine shows an expiration date. This expiration date is valid only if the product has been maintained between 35.6 °F and 46.4 °F (2 °C and 8 °C). While it will not affect the viability of the vaccine, it is not recommended for capsules to be frozen. The product should be stored in a dry place and protected from light.

Temperature:
Store under refrigeration (2 °C to 8 °C).

Light:
Protect from exposure to light.

Moisture:
Protect from moisture.
Protect from high humidity.

Others:
Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

A package of Vivotif® (Typhoid vaccine live oral attenuated Ty21a) contains a single foil blister with 4 enteric-coated capsules (each containing one dose of lyophilized bacteria) for oral administration.

Contents of one enteric-coated capsule of Vivotif®.

Viable *S. typhi* Ty21a 2.0 – 10.0 x 10^9 colony-forming units

Non-viable *S. typhi* Ty21a 5 - 60 x 10^9 bacterial cells

Sucrose 3.3 – 34.2 mg

Amino acid mixture 0.3 - 3.0 mg

Ascorbic acid 0.2 - 2.4 mg

Lactose ad 180 – 200 mg

Magnesium stearate 3.6 - 4.0 mg

Coating Lacquer per capsule:

Hydroxypropylcellulose-phthalate 27 - 33 mg

Diethyl phthalate 6 - 15 mg

Ethylene glycol ≤ 1.5 mg

Composition of the void capsule:

Gelatine Type B 45 - 55 mg

Capsule Cap:

Titanium dioxide
CI 1956, 77891 EEC 171 0.360 - 0.440 mg

Erythrosine FD+C red 3
CI 1956, 45430, EEC 127 0.002 - 0.0024 mg

Yellow Iron Oxide
CI 1956, 77492, EEC 172 0.045 - 0.055 mg

Capsule Body:

Red Iron Oxide
CI 1956, 77491, EEC 172 0.030 - 0.037 mg

Titanium dioxide

CI 1956, 77891 EEC 171 0.540 - 0.660 mg

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Typhoid Vaccine Live Oral Attenuated Ty21a

Biological name: *Salmonella typhi* Ty21a (new nomenclature: *Salmonella enterica* subspecies *enterica* serovar Typhi Ty21a)

Molecular formula and molecular mass: n.a.

Structural formula: n.a.

Physicochemical properties: The lyophilizate of *S. typhi* Ty21a is a strongly hygroscopic powder consisting the stabilizers sucrose, ascorbic acid and an amino acid mixture. The residual water is between 1.5% and 4%.
The lyophilizate is stable at -20 °C ± 5 °C protected from light and humidity for at least 36 months.

CLINICAL TRIALS

Vivotif® (Typhoid vaccine live oral attenuated Ty21a) is a live attenuated vaccine for oral administration. The vaccine contains the attenuated strain *Salmonella typhi* Ty21a.

Salmonella typhi (new nomenclature: *Salmonella enterica* subspecies *enterica* serovar Typhi) is the etiological agent of typhoid fever, an acute, febrile enteric disease. This vaccine will not afford protection against species of *Salmonella* other than *Salmonella typhi* or other bacteria that cause enteric disease.

The incidence of typhoid fever has declined steadily in Canada. Approximately 80 cases are reported annually. Most of these infections were contracted abroad, but a small number occur in Canada, chiefly in areas where sanitation and hygiene are inadequate.[1]

S. typhi is the main causes of typhoid fever, an acute, febrile enteric disease. Typhoid fever continues to be a common infectious disease in many parts of the world. Travelers entering infected areas are at risk of contracting typhoid fever following the ingestion of contaminated food or water. The following regions have a medium to high incidence of typhoid fever: Asia, Africa, Latin America, the Caribbean, Mexico, and Oceania with the exception of Australia and New Zealand. In the United States (US), 74% of new cases were associated with travel outside of the US, even short-term travel, and 84% of these patients had to be hospitalized.[18]

The majority of typhoid cases respond favorably to antibiotic therapy. However, the emergence of chloramphenicol- or ampicillin-resistant strains has greatly complicated therapy. Even with appropriate antibiotic therapy, there were 7 deaths among 901 acute typhoid cases reported in the United States from 1977 - 1979.[19] Approximately 3 - 5% of

acute typhoid cases result in the development of a chronic carrier state.[20] These non-symptomatic carriers are the natural reservoir for *S. typhi* and can serve to maintain the disease in its endemic state or to directly infect individuals.[19] Eradication of the carrier state by antibiotic therapy has been unsuccessful.[21] The effect of immunization with Vivotif® (Typhoid vaccine live oral attenuated Ty21a) on the carrier state is unknown.

Upon ingestion, virulent strains of *S. typhi* are able to pass through the stomach acid barrier, colonize the intestinal tract, penetrate the lumen and enter the lymphatic system and blood stream, thereby causing disease. The risk of severe illness is increased in the absence of gastric acid, e.g. prior gastrectomy, antacid therapy, H_2 antagonist therapy, or in immunocompromised individuals. One possible mechanism by which disease may be prevented is by evoking a local immune response in the intestinal tract. Such local immunity may be induced by oral ingestion of a live attenuated strain of *S. typhi* which causes an aborted infection.

The ability of *S. typhi* to cause disease and to induce a protective immune response is dependent upon the bacteria possessing a complete lipopolysaccharide.[15,16] The *S. typhi* Ty21a vaccine strain, derived by chemical mutagenesis, is entirely deficient in activity of the gal E gene product, which restricts its ability to produce complete lipopolysaccharide. In addition, Ty21a has several nutritional auxotrophies, has approximately half the growth rate of the parent strain Ty2, does not produce H_2S, and lacks the Vi antigen (capsular acidic polysaccharide present on almost all virulent *S. typhi* strains). Ty21a, grown in the presence of low concentrations of galactose, is immunogenic, suggesting that the uptake of galactose by Ty21a enables production of lipopolysaccharide, leading to immunogenicity. It has been presumed that an oversupply of galactose results in accumulation of toxic metabolites within the bacterial cells leading to bacterial lysis. Attenuation and safety of Ty21a have been presumed to be due to the combination of gal E mutation and the lack of Vi antigen. However, an analogous mutant (Vi negative, gal E deletion mutant) of *S. typhi* constructed by recombinant DNA techniques has been shown to be virulent.[17] In addition, galactose induced lysis of Ty21a is inhibited *in vitro* in the presence of glucose. Therefore, the combination of gal E and Vi mutations does not account for the safety of Ty21a or for the failure to recover vaccine organisms from people ingesting the usual dose. Ty21a is attenuated by an incompletely understood mechanism.

The efficacy of the *S. typhi* Ty21a vaccine strain, which is the active ingredient in Vivotif®, has been evaluated in a series of randomized, double-blind, placebo-controlled field trials. A trial was performed in Plaju, Indonesia, with a study population of 20'543 subjects aged 3 - 44 years.[5] The subjects were randomized to receive either 3 doses of vaccine, either in sachets or enteric-coated capsules or an identical appearing placebo. Each dose of vaccine was administered 1 week apart. After 30 months of passive surveillance, vaccine efficacy was determined to be 42% (95% Confidence Interval: 23 - 56.6%) for the enteric-coated capsules(Vivotif® standard formulation) and 53% (95% Confidence Interval: 35.8 - 65.8%) for sachets. The difference in the overall degree of protection conferred against typhoid fever by the 2 different vaccine presentations was not statistically significant. A second trial of a similar design (3 doses administered 1 week apart) was conducted in Santiago, Chile, with a study population of 81'621 school children aged 5 - 19 years.[3] Protection against typhoid fever in all age groups after 36 months of passive surveillance was 33.2% (95% Confidence Interval: 0 - 57%) for the enteric-coated formulation versus 76.9% (95% Confidence Interval: 60 - 87%) for the sachet formulation. The difference in protection rates was highly significant ($p < 0.0001$). This finding can be attributed to the fact that while the sachet formulation afforded significant protection against disease in both young (5 - 9 year old) and older

children (> 9 years of age), but the capsule formulation was ineffective in younger children with this dosage schedule.

The efficacy of the *S. typhi* Ty21a vaccine strain has been evaluated in several additional double-blind, randomized field trials. The first was performed in Alexandria, Egypt, with a study population of 32'388 children 6 - 7 years of age. Three doses of vaccine, in the form of a freshly reconstituted suspension administered after ingestion of 1 g of bicarbonate, were given on alternate days. Immunization resulted in a 95% decrease in the incidence of typhoid fever over a 3 year period of surveillance.[21,22]

A further series of field trials were subsequently performed in Santiago, Chile, to evaluate efficacy where the vaccine was administered only in the form of an acid-resistant enteric-coated capsule. The initial trial involved 82543 5 - 19 year old children, and compared 1 or 2 doses of vaccine given one week apart. After 33 months of passive surveillance, vaccine efficacy was 25% for the single dose schedule and 52% for the 2-dose schedule.[23] A further trial performed in Santiago, Chile, involved 109'594 6 to 21 year old subjects.[24] Three doses of vaccine were administered either on alternate days (short immunization schedule) or 21 days apart (long immunization schedule). Following 36 months of surveillance, vaccination resulted in a 67% decrease in the incidence of typhoid fever in the group taking on an every-other-day dosing schedule for 3 capsules and a 49% reduction in the long immunization schedule group.[24] Following 7 years of surveillance, vaccine efficacy was found to be 62.8% for the short immunization schedule.[4] Next, a field trial was conducted in Santiago, Chile to determine the relative efficacy of two, three and four doses of enteric-coated vaccine administered on alternate days to school-aged children. Because efficacy had already been established in the three dose regimen, a placebo group was not ethically possible. Relative vaccine efficacy, as determined by comparison of disease incidence within the three vaccinated groups, was highest for the four dose regimen. In the group that received four doses, 95.8 cases of typhoid fever were detected per 100,000 study subjects (95% CI = 71 - 121) in comparison to the group that received three doses, in which the incidence of typhoid fever was 160.5 per 100,000 (95% CI = 130 - 191) ($p < 0.004$).[25]

The efficacy of the *S. typhi* Ty21a vaccine strain has been demonstrated only in areas of the world where typhoid fever is endemic. Efficacy has only partially been demonstrated for individuals residing in a non-endemic area who then enter a typhoid fever endemic area.[26,27] It is known that immunization of adult subjects can elicit a humoral anti-*S. typhi* LPS antibody response. Taking advantage of this fact, the seroconversion rate was compared in an open study between adults living in an endemic area (Chile) and non-endemic areas (United States and Switzerland). After the ingestion of three doses of vaccine, comparable seroconversion rates were seen between these groups.

In a study in North American volunteers, protective efficacy of 87% was demonstrated in vaccinated versus control group after challenge with virulent *S. typhi* ($p = 0.0002$).[14] Because of the very low incidence of typhoid fever in residents of North America, efficacy studies are not currently feasible in this population. However, the above observations support the expectation that Vivotif® will provide protection to recipients from non-endemic areas, such as the United States & Canada.

DETAILED PHARMACOLOGY

No formal pharmacology/toxicology studies have been performed with Vivotif® (Typhoid vaccine live oral attenuated Ty21a) in animals except for the standard "General Safety Test", whereby the vaccine is administered to 5 mice and 2 guinea pigs by the intraperitoneal route to detect "abnormal toxicity". This test is performed on each lot of vaccine as part of the final release testing on the final product.

Historically, formal pharmacology/toxicology studies in animals have not been performed for vaccines for the following reasons. First, single and especially multiple dosing regimens can be confounded by the fact that administration of the test compound would, in essence, constitute an immunization and result in a subsequent induction of an antibody response. Therefore, clearance of the compound would be a balance between natural mechanisms and the formation of antibody-antigen complexes. Secondly, such antigen is rapidly cleared by macrophages and lymphocytes as part of the normal immune response mechanism.

MICROBIOLOGY

Not applicable

TOXICOLOGY

No formal pharmacology/toxicology studies have been performed with Vivotif® (Typhoid vaccine live oral attenuated Ty21a) in animals except for the standard "General Safety Test", whereby the vaccine is administered to 5 mice and 2 guinea pigs by the intraperitoneal route to detect "abnormal toxicity". This test is performed on each lot of vaccine as part of the final release testing on the final product.

Long-term animal studies to assess potential carcinogenic or mutagenic properties or adverse effect on fertility have not been performed with Vivotif®.

REFERENCES

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PART III: CONSUMER INFORMATION

Vivotif®

Typhoid Vaccine Live Oral Attenuated Ty21a

This leaflet is part III of a three-part "Product Monograph" published when Vivotif was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Vivotif. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Vivotif (Typhoid Vaccine Live Oral Attenuated Ty21a) is a vaccine for protection of adults and children older than 5 years against typhoid fever, a disease caused by bacteria called *Salmonella enterica* serovar Typhi (abbr. *S. typhi*). You can catch typhoid fever by eating food or drinking water that has been contaminated with the *S. typhi* bacteria. Without antibiotic treatment, typhoid fever can be fatal. The vaccine is intended for persons:

- who travel to or stay in countries where there is a risk of catching typhoid fever
- with ongoing household or intimate exposure to a typhoid carrier
- who work in the laboratory and who frequently handle cultures of *S. typhi*

What it does:

Vivotif is a vaccine that is taken orally to give you protection against typhoid fever. The vaccine is made up of a strain of *S. typhi* that is no longer harmful (*S. typhi* Vaccine Strain Ty21a).

But the body doesn't know that it is not harmful, so it stimulates protective immunity to the typhoid fever bacteria. This protection lasts for 7 years. However, not all vaccinated persons will be fully protected against typhoid fever even after a full course of Vivotif. Therefore, even if you have been vaccinated, you should still take all precautions necessary to avoid food or water that may contain the bacteria that cause typhoid fever.

When it should not be used:

If you have ever had an allergic reaction to any of the ingredients contained in Vivotif.

If you have a poor immune system for any reason.

If you currently have an infection with fever or an illness affecting your gut (such as diarrhoeal illness). Vaccination should be delayed until recovering.

What the medicinal ingredient is:

Typhoid Vaccine Live Oral Attenuated Ty21a

What the important nonmedicinal ingredients are:

Amino acid mixture, ascorbic acid, lactose, magnesium stearate, sucrose.

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

What dosage forms it comes in:

A single foil blister contains 4 capsules (4 doses) in a single package.

Each capsule contains 2.0 – 10.0 x 10^9 live *S. typhi* Ty21a bacteria. The bacteria have been freeze-dried and enclosed in a capsule with a special coating to protect it (enteric coated).

WARNINGS AND PRECAUTIONS

BEFORE you use Vivotif talk to your doctor or pharmacist if:

- you have fever or an illness in your gut.
- you are or think you might be pregnant. Vivotif should be given to a pregnant woman only if clearly needed.
- you are breast-feeding. It is not known if the live bacteria or any other component of Vivotif can pass into breast milk.

INTERACTIONS WITH THIS MEDICATION

Vivotif may not work if taken along with medicines to treat bacterial infections (antibiotics, sulfonamides included). Vivotif should not be given until at least three days after of the last dose of the antibiotic and, if possible, antibiotics should not be started within three days of the last dose of Vivotif.

Alcoholic beverages should not be consumed one hour before or two hours after taking Vivotif.

If you need to take anti malaria tablets containing chloroquine or mefloquine or the combinations atovaquone/proguanil or pyrimethamine/sulfadoxine, these can be taken on the same day as Vivotif. However, if your health care provider gives you any other medicine to prevent malaria, these should not be started until 3 days of the last dose of Vivotif. Likewise, you should wait for 3 days before beginning Vivotif after taking the medicines to prevent malaria.

Oral polio vaccine or yellow fever vaccine can be given while you are taking Vivotif. Injectable vaccines or immunoglobulins may be administered with Vivotif at the same time.

PROPER USE OF THIS MEDICATION

Usual dose:
A day should be selected to take the first capsule (Day 1). The second capsule should be taken on Day 3 (i.e., skip a day after the first capsule), the third capsule should be taken on Day 5 and the fourth capsule should be taken on Day 7.

The foil blister package containing the vaccine capsules should be inspected to ensure that the foil seal and the capsules are intact.

One capsule (each dose) should be swallowed approximately 1 hour before a meal, or two hours after a meal with cold or lukewarm water [temperature not to exceed body temperature, i.e. 37 °C (98.6 °F)]. The vaccine capsule should not be chewed or opened and should be swallowed as soon as possible after placing in the mouth.

Overdose:
Taking doses without skipping a day between doses, will not pose a danger to you. However, you may not be protected against typhoid fever. Therefore, you should tell your doctor or nurse about the mistake in how you have taken the capsules.

Missed Dose:
If you forget to take a dose, you should talk to your health care provider about how long you have missed the recommended dosage regimen.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects were reported most commonly (that is in less than one in ten persons but more than in one in hundred persons) in clinical studies:

Stomach pain, feeling or being sick (nausea and vomiting), diarrhoea, fever, flu-like illness, headache and rash.

Side effects that have been reported very rarely (that is in less than one in ten thousand persons) during normal use include:

Skin irritation, rashes, red or lumpy raised rashes, itching and hives. Severe allergic reactions with drops of blood pressure and loss of consciousness. Weakness, generally feeling unwell, shivering, tiredness, pins and needles, dizziness, joint and muscle pain.

These symptoms disappear spontaneously within a few days. *This is not a complete list of side effects. For any unexpected effects while taking Vivotif, contact your doctor or pharmacist.*

HOW TO STORE IT

Keep Vivotif out of the reach and sight of children.

Vivotif is not stable when exposed to room temperature.

Vivotif should be stored at refrigerated temperatures between 35.6 °F and 46.4 °F (2 °C and 8 °C). Vaccine capsules should be stored between doses in the refrigerator. The vaccine may be out of refrigeration during a reasonable transit time home from the clinic. If the capsules are left outside of refrigeration at room temperature 77 °F (25 °C) for up to 12 hours on a one-time only occasion, the product quality will not be affected, and the capsules can still be taken. Each blister of vaccine shows an expiration date. This expiration date is valid only if the product has been maintained between 35.6 °F and 46.4 °F (2 °C and 8 °C). The product should be stored in a dry place and protected 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: 866-844-0018

By toll-free fax: 866-844-5931

Email: caefi@phac-aspc.gc.ca

Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, A/L 6502A
Ottawa, ON K1A 0K9

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

For more information or safety reporting please contact:
medical.information_NA@bavarian-nordic.com or call the toll-free-number: 1 833-203-7933

This leaflet was prepared by Bavarian Nordic A/S
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