1. NAME OF THE MEDICINAL PRODUCT

Vivotif

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains not less than $2x10^9$ CFU of viable Salmonella Typhi Ty21a cells (also known as *Salmonella enterica* serovar Typhi , abbr. *S.* Typhi).

Excipients with known effect: lactose, sucrose.

For the full list of excipients , see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant hard capsules.

The capsules are bicoloured: the capsule cap is opaque orange and the capsule body is opaque white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vivotif is indicated for active oral immunisation against typhoid fever, caused by Salmonella enterica serovar Typhi, (S. Typhi), in adults and children aged five years and older.

This vaccine should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

One capsule of Vivotif is taken on each of Days 1, 3 and 5.

Complete vaccination comprises the ingestion of three capsules as described above. The optimal immune response may not be achieved unless the entire vaccination schedule is completed.

Protection against typhoid fever commences approximately seven to ten days after ingesting the third dose of vaccine. The entire vaccination schedule should be completed at least one week prior to travel to an endemic area.

Revaccination

Revaccination is recommended at three years following the most recent vaccination for all individuals.

Revaccination comprises the ingestion of three capsules on Days 1, 3, and 5, as for the original vaccination schedule.

Paediatric Population

Vivotif is not indicated for children under 5 years of age.

The posology in children is the same as in adults. Safety and efficacy in children under five years of age have not been established.

Method of administration

One capsule of Vivotif is taken with cold or lukewarm water (temperature not more than 37°C) on an empty stomach and at least one hour before the next meal. The vaccine capsule should not be chewed and should be swallowed as soon as possible after placing in the mouth.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Allergic reaction to previous ingestion of the product.

Congenital or acquired immune deficiency (including patients receiving immunosuppressive or antimitotic drugs).

Acute febrile illness or acute gastrointestinal illness. Vaccination should be postponed until after recovery.

4.4 Special warnings and precautions for use

Vivotif does not provide 100% protection against typhoid fever. Vaccinees should adhere to hygiene advice and exercise caution regarding food and water consumed in typhoid-affected areas.

The capsules contain lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption, fructose intolerance, or sucrase-isomaltase insufficiency should not take this vaccine.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccination with Vivotif should be postponed during and for at least three days before and after antibiotic or antibacterial sulfonamide treatment, due to possible inhibition of the growth of the vaccine organisms and potential attenuation of the immune response. A longer interval should be considered for long-acting antibiotics (e.g., azithromycin).

Combination with malaria prophylaxis

If malaria prophylaxis is needed, it is recommended to complete the vaccination with Vivotif prior to malaria prophylaxis. In this case, an interval of at least three days should be kept between the last dose of Vivotif and the start of malaria prophylaxis.

Vivotif may be administered concomitantly with yellow fever vaccine, CVD 103-HgR cholera vaccine and oral polio vaccine. No data are available regarding interaction between Vivotif and other live attenuated vaccines.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal reproduction studies have not been conducted with Vivotif. It is not known whether Vivotif causes foetal harm when administered to pregnant women or can affect reproduction capacity. Vivotif should not be administered during pregnancy unless clearly needed, like in cases of increased risk of infection.

Breast-feeding

There are no data regarding administration of Vivotif to nursing mothers. S. Typhi Ty21a is not absorbed systemically, therefore it is not expected to be excreted in human milk. Vivotif should not be administered during breast-feeding unless clearly needed, like in cases of increased risk of infection.

Fertility

It is not known whether Vivotif can affect reproductive capacity.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, some of the undesirable effects mentioned under section 4.8 may temporarily affect the ability to drive or operate machinery.

4.8 Undesirable effects

Summary of safety profile

During clinical trials over 1.4 million capsules of Vivotif were administered. Since initial registration the number of doses distributed exceeds 100 million. The most frequent adverse reactions have been abdominal pain, nausea, headache, fever, diarrhoea, vomiting, and skin rash. Most adverse reactions have been mild. One isolated, non-fatal anaphylactic shock considered to be an allergic reaction to the vaccine was reported.

The adverse reaction frequency classification used is as follows: Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Tabulated summary of adverse reactions

Adverse reactions occurring in clinical trials were as follows:

Adverse Reactions	**Frequency**
Nervous system disorders	
Headache	Common
Gastrointestinal disorders	
Abdominal pain, nausea, vomiting, diarrhoea	Common
Skin and subcutaneous tissue disorders	
Rash	Common
General disorders and administration site conditions	
Pyrexia	Common

Adverse reactions reported during post-marketing surveillance are as follows:

Adverse Reactions*
Immune system disorders
Hypersensitivity, anaphylactic reaction, including shock
Metabolism and nutrition disorders
Decreased appetite
Nervous system disorders
Paraesthesia, dizziness
Gastrointestinal disorders
Flatulence, abdominal distension
Skin and subcutaneous tissue disorders
Dermatitis, pruritus, urticaria
Musculoskeletal and connective tissue disorders

Arthralgia, myalgia, back pain
General disorders and administration site conditions
Asthenia, malaise, fatigue, chills, influenza-like illness

*Because these reactions are reported spontaneously during post-marketing from a population of unknown size, it is not possible to establish their frequency. Therefore, the frequency of these reactions is not known.

Paediatric Population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/
Additionally, you should also report to Kamada LTD to email address:
pharmacovigilance@kamada.com

4.9 Overdose

Occasional reports of overdose have been received, i.e. consumption of two or more capsules at the same time. The symptoms reported were not different from those at the recommended dosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacterial vaccines, ATC code: J07AP01

Mechanism of action

In contrast to virulent S. Typhi which can cause systemic disease, the vaccine strain Ty21a is attenuated as a result of the absence of the Vi capsular polysaccharide virulence factor and the galE mutation which causes irreversible changes in cell wall biosynthesis. The galE mutation limits replication in vivo owing to an accumulation of toxic metabolites, which causes lysis of the bacterial cell. The vaccine strain Ty21a thus remains locally in the intestine and can not be detected systemically or in the stools following ingestion of the usual dose. Ty21a triggers humoral and cellular immunity both locally and systemically. Specifically, Ty21a induces IgA to Salmonella O antigen, as well as antibody-secreting cells (ASCs) and polyfunctional CD4+ and CD8+ T cells with a gut-homing phenotype. IgA and CD8+ responses can be detected in the gastrointestinal tract up to 2 years after Ty21a vaccination.

A non-placebo-controlled challenge study in US subjects was conducted with an early formulation and dose regimen of Ty21a which demonstrated 87% protection against virulent S. Typhi following vaccination.

Clinical protection against other enteric fever-causing agents including S. Paratyphi has not been shown in randomised, controlled clinical trials.

The three-dose regimen of enteric-coated capsules in an every other day schedule has been shown in a field trial to have a protective efficacy of 71% (95% CI 35%-87%) during the first year after

vaccination, 67% (95% CI 47%-79%) over three years and 62% (95% CI 48%-73%) protection over seven years of follow-up.

Complete vaccination comprises the ingestion of three capsules at Days 1, 3 and 5. The optimal immune response may not be achieved unless the entire vaccination schedule is completed. Two doses were shown to have an efficacy of 59% (95% CI 41%-71%) and one dose had an efficacy of 29% (95% CI 4%-47%) over two years of follow-up.

Revaccination studies in healthy volunteers demonstrated that local humoral and cell-mediated immunity induced by the primary vaccination persists for at least three years. The clinical relevance of these observations are unclear as no immunological correlate of protection exists. A field study conducted in a typhoid-endemic region demonstrated protection at 62% (95% CI 48%-73%) over seven years post vaccination.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

No preclinical safety data are available for Vivotif.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients contained in the preparation are as follows:
Lactose anhydrous
Sucrose
Magnesium stearate (E470)
Casein acid hydrolysate
Ascorbic acid (E300)

Capsule coating:
Hydroxypropylmethylcellulose phthalate
Diethyl phthalate
Ethylene glycol

Capsule cap:
Gelatin
Titanium dioxide (E171)
Yellow Iron Oxide (E172)
Red Iron Oxide (E172)
Erythrosine (E127)

Capsule body:
Gelatin
Titanium dioxide (E171)

The vaccine also contains inactivated Salmonella Typhi Ty21a cells.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Carton box with one blister pack. Each blister pack contains three capsules. Pack size: 3 doses.
Blister pack is composed of plastic film (PVC/PE/PVDC) and aluminium foil.

6.6 Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Bavarian Nordic Berna GmbH
Oberriedstrasse 68, 3174 Thörishaus, Switzerland

8. MARKETING AUTHORISATION HOLDER

Kamada Ltd
Beit-Kama, MP NEGEV 8532500, Israel

9. MARKETING AUTHORISATION NUMBER

167-32-36273

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