1. Name of the medicinal product

TYPHIM Vi

2. Qualitative and quantitative composition

One dose of 0.5 mL of vaccine contains: Polysaccharides of Salmonella typhi (Ty2 strain) 25 micrograms. For excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection in a prefilled syringe. Solution for injection in a multidose vial

4. Clinical particulars

4.1 Therapeutic indications

Prevention of typhoid fever in adults and in children over 2 years of age, and especially: travellers to endemic areas, migrants, health care professionals and military personnel.

4.2 Posology and method of administration

Posology

RESTRICTED TO ADULTS AND CHILDREN OVER TWO YEARS OF AGE.

A single injection ensures protection. Revaccination should be performed every 3 years if the risk of exposure continues.

The vaccination schedule is the same for children and for adults.

Method of administration

Intramuscular or subcutaneous route.

4.3 Contraindications

. Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any residual substances that may be present as traces such as formaldehyde or casein.
Vaccination must be postponed in case of febrile or acute disease.

4.4 Special warnings and precautions for use

This vaccine provides protection against the risk of infection related to Salmonella typhi but gives no protection against Salmonella paratyphi A or B or against non-typhoidal Salmonellae.
Prior to administration of TYPHIM Vi, the recipient or their guardian must be asked about the recipient's personal history, current health status and any adverse event after previous immunisations. In subjects who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, the need for the vaccination must be carefully considered, following a risk-benefit assessment.
As with all vaccines, facilities for the management of anaphylaxis should always be available during vaccination. As a precautionary measure, epinephrine injection (1:1000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.
Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

As with all injectable vaccines, TYPHIM Vi must be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following intramuscular administration to these subjects.
As with any vaccine, vaccination with TYPHIM Vi may not result in protection in all vaccine recipients.
The immunogenicity of TYPHIM Vi may be reduced by immunosuppressive treatment or immunodeficiency. In such cases it is recommended to postpone vaccination until the end of the disease or treatment. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited.
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded

4.5 Interaction with other medicinal products and other forms of interaction

Separate injection sites must be used in case of concomitant vaccine administration.
TYPHIM Vi may be administered during the same vaccination session with other common vaccines (yellow fever, diphtheria, tetanus, poliomyelitis, rabies prepared on Vero cells, meningitis A+C, hepatitis A and hepatitis B).

4.6 Pregnancy and lactation

Pregnancy
Animal reproduction studies have not been conducted with TYPHIM Vi.
Data on the use of this vaccine in pregnant women are limited. Therefore the administration of the vaccine during pregnancy is not recommended. TYPHIM Vi should be given to pregnant women only if clearly needed and following an assessment of the risks and benefits.Lactation
It is not known whether this vaccine is excreted in human milk. Caution must be exercised when TYPHIM Vi is administered to a nursing mother

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Tiredness has been observed as a very rare reaction following administration of this vaccine (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile
During clinical development, more than 15,000 people received TYPHIM Vi (first or second injection).
The most common adverse reactions, in all age groups, were injection site pain. In adults from 18 years of age, myalgia and fatigue were the most frequently reported systemic reactions. In children and adolescents (from 2 to 17 years of age), myalgia and headache were the most frequently reported systemic reactions.
Most adverse reactions appeared within 3 days after vaccination. Most reactions resolved spontaneously within 1 to 3 days after onset.
b. Tabulated list of adverse reactions
The adverse reactions come from clinical studies (pooled analysis) and worldwide post-marketing experience. The pooled analysis has been performed on 6 recent studies sharing the same safety standard integrating data from 1532 subjects (97 children and adolescents from 2 to 17 years of age and 1435 adults).
In each System Organ Class, the adverse reactions are ranked under headings of frequency, the most common reactions coming first, using the following convention:
Very common (≥1/10) Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100) Rare (≥1/10 000 to <1/1000)

Very rare (<1/10 000) including isolated cases
Not known (cannot be estimated from the available data).

The table below summarizes the frequencies of the adverse reactions that were recorded after any dose of TYPHIM Vi in children and adolescents from 2 to 17 years of age and adults.

Adverse Reactions Experienced	**Children and Adolescents** 2-17 years	**Adults** ≥ 18 years
	Frequency	Frequency
Immune system disorders		
Anaphylactic, anaphylactoid reactions, including shock	Not known*	
Serum sickness disease	Not known*	
Nervous system disorders		
Vasovagal syncope in response to injection	Not known*	
Headache	Very common	Common
Respiratory, thoracic and mediastinal disorders		
Asthma	Not known*	
Gastrointestinal disorders		
Nausea	Not known*	
Vomiting	Not known*	
Diarrhoea	Not known*	
Abdominal pain	Not known*	
Skin and subcutaneous tissue disorders		
Allergic type reactions such as pruritus, rash, urticaria	Not known*	
Musculoskeletal and connective tissue disorders		
Arthralgia	Not known*	
Myalgia	Very common	Very common
General disorders and administration site condition		
Injection site pain	Very common	
Injection site erythema	Very common	Common
Injection site pruritus	-	Uncommon
Injection site swelling/oedema/ induration	Very common	Common
Malaise	Common	Very common
Fever	Common	-
Fatigue/asthenia	Common	Very common

* reported during postmarketing surveillance

The most frequently reported adverse reactions in children and adolescents (from 2 to17 years of age) were injection site reactions: pain (52.6%), swelling/oedema/ induration (16.5%) and erythema (14.4%). The most frequently reported systemic reactions were myalgia (14.6%) and headache (13.5%).

In adults from 18 years of age, the most frequently reported adverse reaction were injection site pain (75.6%), myalgia (47.1%) and fatigue/asthenia (25.0%).

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 (www.health.gov.il) according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Not applicable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Typhoid vaccines, ATC code: J07AP03
This vaccine contains purified Vi capsular polysaccharide of *Salmonella typhi* (Ty 2 strain). Immunity appears within 1-3 weeks after injection and lasts around 3 years.
A double-blind, randomized, controlled efficacy clinical trial was conducted in a highly endemic area in Nepal, in both paediatric and adult populations. A total of 3,457 subjects received TYPHIM Vi. The level of protection conferred by a single dose of the vaccine was 74% against blood culture-confirmed cases of typhoid fever throughout the 20 months of active surveillance when compared with the control group.
Seroconversion rate (defined as 4-fold rise of anti-Vi antibody levels) was collected in 19 clinical trials. These trials were conducted in endemic and non-endemic areas in both paediatric and adult populations representing a total of 2,137 evaluable subjects. In adult population, seroconversion rate ranged from 62.5% to 100% four weeks after a single injection, with similar magnitude of anti-Vi immune response in non- endemic areas compared to endemic areas.
Anti-Vi antibody persistence depends on endemicity, with a trend for better persistence in endemic areas (documented up to 10 years in 83 children at levels equal or above serological correlate of protection of 1 µg/mL). In non-endemic areas, anti-Vi antibodies persist for 2 to 3 years. Revaccination should be carried out with an interval of not more than 3 years in subjects who remain at risk of exposure to typhoid fever.

Paediatric population
In a double-blind, randomized, controlled efficacy clinical trial conducted in a highly endemic area in South Africa, a total of 5,692 paediatric subjects from 5 to 15 years of age received TYPHIM Vi. The level of protection conferred by a single dose of the vaccine was 55% against blood culture- confirmed cases of typhoid fever during the 3-year follow-up period when compared with the control group.
Immunogenicity was assessed in both endemic and non-endemic areas in paediatric population aged from 2 to 17 years. In 9 clinical trials representing a total of 733 evaluable children four weeks after a single injection of TYPHIM Vi, seroconversion rate ranged from 67% to 100%, demonstrating similar magnitude of anti-Vi immune response to what was documented with adult participants

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Phenol (preservative)
Isotonic buffer solution*
*Composition of the isotonic buffer solution:
Sodium Chloride
Disodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Solution for injection in a multi-dose vial: any opened vials remaining at the end of the immunization session (within six [6] hours of first opening), should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C -8°C). Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.5 mL of solution in a prefilled syringe (type I glass) with a plunger stopper - Boxes of 1 and 20.
20 doses x 0.5 mL of solution in a vial of 10 ml (glass) with a stopper (chlorobutyl) - Box of 1 or 10 vials
Not all pack sizes and presentations may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be visually inspected before administration for discolouration or any particulate matter. Shake well immediately before use.
For needle free syringes, the needle should be pushed firmly on to the end of the pre-filled syringe and rotated through 90 degrees.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

SANOFI PASTEUR, 14 ESPACE HENRY VALLÉE, 69007 LYON, FRANCE

8. LICENSE HOLDER

Medici Medical Ltd., 3 Hamachshev St., Netanya 4250713

9. MARKETING AUTHORISATION NUMBERS

125-66-28629-00

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