ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TYPHIM Vi, solution for injection in prefilled syringe.

Polysaccharide typhoid vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose of 0.5 mL of vaccine contains:

Polysaccharides of *Salmonella typhi* (Ty2 strain) .....25 micrograms

For the full list of excipients, see section 6.1.

Typhim Vi may contain traces of formaldehyde or casein, which are used during the manufacturing process (see section 4.3).

3. PHARMACEUTICAL FORM

Solution for injection in prefilled syringe.

Clear, colourless solution.

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 2 YEARS OF AGE.

A single injection ensures protection. If exposure to risk continues and depending on the level of exposure, revaccination will be performed every 2 to 3 years.

Paediatric population

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, to formaldehyde or to casein (which may be present as traces in each dose, owing to their use during the manufacturing process).

Vaccination should be postponed in case of acute febrile disease.

4.4 Special warnings and precautions for use

Do not inject by the intravascular route.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection, especially in adolescents. This may be accompanied by several neurological signs such as transient sight disorders, paraesthesia and tonic-clonic limb movements during the recovery phase. It is important that procedures be in place to avoid any injury from faints.

This vaccine protects against the risks of infection by *Salmonella typhi* but not against *Salmonella paratyphi* A or B or non-typhoidal salmonella.

The immunogenicity of TYPHIM Vi may be reduced by immunosuppressive treatment or immunodeficiency. It is then recommended to wait until the end of the treatment or disease before vaccinating. Nevertheless, vaccination of subjects with chronic immunodeficiency, such as HIV infection, is recommended even if the immune response may be limited.

Injection must be performed via the subcutaneous route in subjects with thrombocytopenia or bleeding disorders.

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

Paediatric population

This vaccine is not indicated in children under 2 years of age because of the risk of insufficient antibody response.

TYPHIM Vi contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

Traceability:

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

This vaccine can be associated with other common vaccines (hepatitis A, yellow fever, diphtheria, tetanus, poliomyelitis, rabies, meningitis A + C and hepatitis B) during the same vaccination session, using separate injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

No reliable animal teratogenic data are available.

Currently, no sufficiently relevant clinical data are available to assess a potential teratogenic or foetotoxic effect of this vaccine when administered during pregnancy.

Because of the seriousness of the disease, and in case of high risk of exposure to typhoid fever, pregnancy is not an obstacle to the vaccination protocol.

Lactation

This vaccine can be used during lactation.

4.7 Effects on ability to drive and use machines

The effects on the ability to drive and use machines have not been studied.

4.8 Undesirable effects

a. Summary of the safety profile

More than 15,000 subjects received TYPHIM Vi (either in a single injection or as a second injection) in clinical studies.

The most common adverse reaction, in all age groups, was 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 cephalalgia were the most frequently reported systemic reactions.

Most adverse reactions occurred within three days of vaccination. Most reactions resolved spontaneously within 1 to 3 days after onset.

b. Tabulated list of adverse reactions

The adverse reactions listed below come from clinical studies (pooled analysis) and worldwide post-marketing experience. The pooled analysis was performed on 6 recent studies sharing the same safety standard integrating data from 1532 subject (97 children and adolescents from 2 to 17 years of age and 1435 adults).

In each System Organ Class, the adverse events 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 available data.

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

Adverse reactions	**Children and Adolescents 2-17 years (N=97)**	**Adults ≥ 18 years (N=1435)**
	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*	
Cephalalgia	Very common	Common
Respiratory, thoracic and mediastinal disorders		
Asthma	Not known*	
Gastrointestinal disorders		
Nausea	Not known*	

Adverse reactions	Children and Adolescents 2-17 years (N=97)	Adults ≥ 18 years (N=1435)
	Frequency	Frequency
Vomiting	Not known*	
Diarrhoea	Not known*	
Abdominal pain	Not known*	
Skin and subcutaneous tissue disorders		
Allergic-like reactions such as pruritus, skin rash, urticaria	Not known*	
Musculoskeletal and connective tissue disorders		
Arthralgia	Not known*	
Myalgia	Very common	Very common
General disorders and administration site conditions		
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 post-marketing surveillance

The most frequently reported adverse reactions in children and adolescents (from 2 to 17 years of age) were injection site reactions: pain (52.6%), swelling / œdema / induration (16.5%) and erythema (14.4%). The most frequently reported systemic reactions were myalgia (14.6%) and headaches (13.5%).

In adults from 18 years of age, the most frequently reported adverse reactions 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: "Agence nationale de sécurité du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance - Site internet: www.signalement-sante.gouv.fr."

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: bacterial vaccines, ATC code: J07AP03.

This vaccine is prepared from purified Vi capsular polysaccharides of *Salmonella typhi*. Immunity appears between 1 to 3 weeks after the injection. Protection lasts around 3 years.

A double-blind, randomized, controlled efficacy clinical study was conducted in a highly endemic area in Nepal, in children and adults from 5 to 44 years. A total of 3,457 subjects received TYPHIM Vi. Compared with the control group (23 valence-pneumococcal polysaccharide vaccine), vaccine efficacy conferred by a single dose of vaccine TYPHIM Vi was 74% (CI 95%: 49; 87) against blood culture-confirmed cases of typhoid fever throughout the 20 months of active surveillance.

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 adults and children from 2 years of age representing a total of 2,137 evaluable subjects. In the adult population, the seroconversion rate ranged from 62.5% to 100% three to 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 1 µg/mL considered as a serological indicator of protection against typhoid fever). In non-endemic areas, anti-Vi antibodies persist for 2 to 3 years with rates above 1 µg/mL around 41% after two years and 35.6% after 3 years of vaccination with TYPHIM Vi. Revaccination should be carried out with a maximum interval of 3 years if the subject is still exposed to the risk.

Paediatric population

In a double-blind, randomized, controlled efficacy clinical study conducted in a highly endemic area in South Africa, a total of 5,692 subjects from 5 to 15 years of age received TYPHIM Vi. Compared with the control group (meningococcal polysaccharide vaccine of groups A and C), vaccine efficacy conferred by a single dose of vaccine TYPHIM Vi was 55% (CI 95% : 30 ; 71) against blood culture- confirmed cases of typhoid fever during a 3-year follow-up.

Immunogenicity was assessed in both endemic and non-endemic areas in paediatric population aged from 2 to 17 years. In 9 clinical studies including 733 evaluable children, three to four weeks after a single injection of TYPHIM Vi, the seroconversion rate ranged from 67% to 100%, with a magnitude of anti-Vi immune response similar to that documented in adult.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of acute toxicity, repeat dose toxicity, local safety and hypersensitivity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol and a buffer solution containing sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate and water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

6.5 Nature and contents of container

0.5 mL of solution in prefilled syringe (type I glass) with a plunger stopper (chlorobutyl). Box of 1 and 20.

0.5 mL of solution in prefilled syringe (type I glass) with a plunger stopper (chlorobutyl), a tip-cap (synthetic isoprene-bromobutyl), without needle. Box of 1.

0.5 mL of solution in prefilled syringe (type I glass) with a plunger stopper (chlorobutyl), a tip-cap (synthetic isoprene-bromobutyl), with 1 to 2 separate needles. Box of 1.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be kept at room temperature for a few minutes before use.

For syringes without attached needles, the separate needle must be fitted firmly to the syringe, rotating it by a one quarter turn.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR
14 ESPACE HENRY VALLÉE
69007 LYON
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 339 841 1 3: 0.5 mL of solution in prefilled syringe (type I glass) with a plunger stopper (chlorobutyl). Box of 1.
- 34009 331 507 5 4: 0.5 mL of solution in prefilled syringe (type I glass) with a plunger stopper (chlorobutyl). Box of 20.
- 34009 369 928 8 7: 0.5 mL of solution in prefilled syringe (type I glass) with a plunger stopper (chlorobutyl), a tip-cap (synthetic isoprene-bromobutyl), without needle. Box of 1.
- 34009 369 929 4 8: 0.5 mL of solution in prefilled syringe (type I glass) with a plunger stopper (chlorobutyl), a tip-cap (synthetic isoprene-bromobutyl), with one separate needle. Box of 1.
- 34009 369 930 2 0: 0.5 mL of solution in prefilled syringe (type I glass) with a plunger stopper (chlorobutyl), a tip-cap (synthetic isoprene-bromobutyl), with two separate needles. Box of 1.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

[to be completed subsequently by the Marketing Authorisation Holder]

10. DATE OF REVISION OF THE TEXT

[to be completed subsequently by the Marketing Authorisation Holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.