Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ViATIM, Suspension and solution for suspension for injection in pre-filled syringe. Hepatitis A (inactivated, adsorbed) and Typhoid polysaccharide vaccine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The dual-chamber syringe contains 0.5 millilitre of inactivated hepatitis A vaccine and 0.5 millilitre of typhoid polysaccharide vaccine which are mixed prior to administration.

After reconstitution, 1 dose (1ml) contains:

Originally contained in the suspension:
Hepatitis A virus, GBM strain (inactivated)[1,2].....160 U[3]
[1] produced in human diploid (MRC-5) cells
[2] adsorbed on aluminium hydroxide, hydrated (0.3 milligrams Al)
[3] In the absence of an international standardised reference, the antigen content is expressed using an in-house reference

Originally contained in the solution:
Salmonella typhi (Ty 2 strain) capsular Vi polysaccharide.....25 micrograms

Excipient(s) with known effect (see Section 4.4):
Phenylalanine.....10 micrograms

For the full list of excipients, see section 6.1.
ViATIM may contain traces of neomycin, which is used during the manufacturing process (see section 4.3).

3 PHARMACEUTICAL FORM

Suspension and solution for suspension for injection in pre-filled syringe.

The inactivated hepatitis A vaccine is a cloudy and white suspension and the typhoid polysaccharide vaccine is a clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ViATIM is indicated for simultaneous active immunisation against typhoid fever and hepatitis A virus infection in subjects from 16 years of age.
ViATIM should be given in accordance with official recommendations.

4.2 Posology and method of administration

Posology
The recommended dosagefor subjects of at least 16 years of age is 1 millilitre of the mixed vaccine.
Initial protection is achieved with one single dose of ViATIM. Protective levels of antibody may not be reached until 14 days after administration of the vaccine.
In order to provide long-term protection against infection caused by the hepatitis A virus, a second dose (booster) of an inactivated hepatitis A vaccine should be given. ViATIM may be used to provide one or both doses of hepatitis A vaccine as follows:
• In subjects who have received one dose of ViATIM:
- either a dose of monovalent hepatitis A vaccine should be given within 36 months and preferably within 6 to 12 months (see section 5.1)

- or, if continued protection against typhoid is also required, a second dose of ViATIM may be given provided that approximately 36 months have elapsed since the first dose.
• In subjects who have received one dose of monovalent hepatitis A vaccine:
- ViATIM may be used to provide the second dose (booster) of hepatitis A vaccine if protection against typhoid fever is also desirable. It should be given within 36 months of the hepatitis A vaccine and preferably within 6 to 12 months.

It is predicted that HAV antibodies persist for many years (beyond 10 years) after the second dose (booster).
In subjects who remain at risk of typhoid fever, revaccination against typhoid fever should be carried out with a single dose of a typhoid Vi polysaccharide vaccine every 3 years (see section 5.1).
Paediatric population
The safety and efficacy of ViATIM in children and adolescents below 16 years have not yet been established. No data are available.
Method of administration
ViATIMshould be administered by slow intramuscular injection in the deltoid region.
ViATIMmustnot be administered intravascularly.
ViATIMshould not be administered into the buttocks due to the varying amount of fatty tissue in this region, nor by the intradermal route, since these methods of administration may induce a weaker immune response. ViATIMmay be administered by the subcutaneous route in patients with thrombocytopenia or in those at risk of haemorrhage.
For instructions for preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 or to neomycin (present in trace amounts as a residual of the manufacturing process).
Vaccination should be delayed in subjects with an acute severe febrile illness.

4.4 Special warnings and precautions for use

As with all vaccines, appropriate facilities and medication such as epinephrine (adrenaline) should be readily available for immediate use in case of anaphylaxis or hypersensitivity following injection.
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.
Immunogenicity of ViATIM could be impaired by immunosuppressive treatment or in immunodeficient subjects. It is recommended to delay vaccination until the completion of any immunosuppressive treatment. Subjects with chronic immunodeficiency such as HIV infection may be vaccinated if the underlying immunodeficiency allows the induction of an antibody response, even if limited.
Because of the incubation period of hepatitis A disease, infection may be present but not clinically apparent at the time of vaccination. It is not known whether ViATIMwill prevent hepatitis A in this case.
ViATIM does not protect against infection caused by other known liver pathogens including hepatitis B, hepatitis C and hepatitis E viruses.
ViATIMdoes not protect against infection by *Salmonella enterica* other than serotype *typhi*.
As with any vaccine, a protective immune response may not be elicited in all vaccinees.
ViATIM contains phenylalanine, ethanol, potassium and sodium

- ViATIM contains 10 microgram phenylalanine in each 1 ml dose which is equivalent to 0.17 microgram/kg for a 60 kg person. Phenylalanine may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
- ViATIM contains 2 mg of alcohol (ethanol) in each 1 ml dose. The small amount of alcohol in this medicine will not have any noticeable effects.
- ViATIM contains less than 1 mmol potassium (39 mg) and less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'potassium-free' and '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 interactions

ViATIMmust not be mixed with any other vaccine in the same syringe.
Concomitant administration of ViATIM with the combined, adsorbed, tetanus, low dose diphtheria and inactivated poliomyelitis vaccine (Td-IPV) at two separate sites demonstrated non-inferiority compared to the separate administration of the two vaccines at different time points for all valences, except for the Vi valence, in terms of immune response obtained one month after vaccination. Nevertheless, anti-Vi seroconversion rate (≥ 4-fold rise) for concomitant administration was non-inferior to the separate administration in subjects who were not seroprotected before vaccination (see section 5.1). Since the seroprotection rate (the percentage of subjects reaching the threshold of protection for anti-Vi antibodies ≥1 microgram/mL) was consistent with the expected range of responses when ViATIM is given alone, it is unlikely that concomitant administration of ViATIM and the Td-IPV at different sites will have clinical consequences. Therefore, concomitant administration of ViATIM with the Td-IPV at two separate sites can be performed.
No interaction studies have been performed with ViATIM and other inactivated vaccines. However, based on data obtained from the concomitant administration of the monovalent typhoid Vi polysaccharide vaccine with diphtheria-tetanus (DT), tetanus-inactivated poliomyelitis (T-IPV), rabies, meningococcal polysaccharide A/C and hepatitis B vaccines and from the concomitant administration of the monovalent inactivated hepatitis A vaccine with hepatitis B vaccines, no interference with the immune responses to any of these antigens would be expected.
Concomitant administration of yellow fever vaccine with ViATIM has not been specifically assessed.However, based on data obtained from the concomitant administration of the monovalent vaccines (typhoid Vi polysaccharide vaccine and inactivated hepatitis A vaccine) with yellow fever vaccine, no interference with the immune responses to any of these antigens would be expected.
The effect of concomitant administration of immunoglobulins on the immunogenicity of ViATIM has not been assessed. Therefore, interference with the immune response of ViATIM cannot be ruled out. Data obtained from concomitant administration of immunoglobulins with the monovalent inactivated hepatitis A vaccine showed that anti-HAV seroconversion rates were not modified whereas anti-HAV antibody titres could be lower than after vaccination with the monovalent vaccine alone.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a limited number (more than 150 cases with monovalent typhoid Vi polysaccharide vaccine, more than 40 cases with monovalent inactivated hepatitis A vaccine and more than 10 cases with ViATIM or the two components given simultaneously) of exposed pregnancies indicate no adverse effects of ViATIMon pregnancy or on the health of the foetus/new born child. To date no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).
Caution should be exercised when prescribing to pregnant women.
When the patient is considered to be at risk of only one of hepatitis A or typhoid fever, the monovalent vaccine should be used.
Breast-feeding
It is unknown whether ViATIM is excreted in human breast milk. The excretion of ViATIM in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to administer or not administer ViATIM should be made taking into account the benefit of breast-feeding to the child and the benefit of ViATIM to the woman.
Fertility
No fertility data are available.

4.7 Effects on ability to drive and use machines

ViATIM has a minor influence on the ability to drive and use machines.
Dizziness has been observed as an uncommon reaction (≥1/1000, <1/100) following administration of this vaccine (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile
During clinical studies, the most commonly reported reactions were those occurring at the injection site.

Pain at the ViATIM injection site was reported in 89.9% of subjects (severe in 4.5%). For subjects who received the two monovalent vaccines concomitantly at separate injection sites, pain was reported in 83.2% of subjects (severe in 5.0%) for both vaccine sites combined. Pain was reported by 79.3% of subjects (severe in 5.0%) at the Vi vaccine site and by 50.3% of subjects (severe in 0.6%) at the hepatitis A vaccine site.

Pain at the injection site lasting more than 3 days was reported by 17.4% of subjects after ViATIM, by 2.8% of subjects for the monovalent Vi vaccine site and by 0.6% of subjects for the monovalent hepatitis A vaccine site.

Severe oedema/induration (> 5 cm) was reported in 7.9% of subjects at the ViATIM site. For subjects who received the two monovalent vaccines concomitantly at separate injection sites, severe oedema/induration was reported in 1.7% of subjects for both vaccine sites combined (in 1.1% of subjects at the Vi vaccine site and in 0.6% of subjects at the hepatitis A vaccine site).

The overall incidence of systemic reactions was similar between subjects who were vaccinated with ViATIM and subjects who received the two monovalent vaccines concomitantly at separate injection sites.

All reactions resolved without any sequelae.

b. Tabulated list of adverse reactions
Adverse reaction data are derived from clinical trials and worldwide post marketing experience.

Within each system organ class the adverse reactions are ranked under headings of frequency, most frequent reactions first, using the following convention:
Very common (≥1/10),
Common (≥1/100, <1/10),
Uncommon (≥1/1000, <1/100),
Rare (≥1/10,000, <1/1000),
Very rare (<1/10,000),
Not known: cannot be estimated from the available data. Based on spontaneous reporting, these adverse events have been very rarely reported following commercial use of ViATIM. Because events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Immune system disorders
Not known: anaphylactic/anaphylactoid reactions, including shock; serum sickness.

Nervous system disorders
Very common: headache.
Uncommon: dizziness.
Not known: vasovagal syncope in response to injection, paraesthesia.
Gastrointestinal disorders
Common: nausea, diarrhoea.
Not known: vomiting, abdominal pain.

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash.
Not known: urticaria.

Musculoskeletal and connective tissue disorders
Very common: myalgia.
Common: arthralgia.

General disorders and administration site conditions
Very common: malaise, asthenia, injection site disorders (pain, induration, oedema, erythema).
Common: fever.

Investigations
Not known: transaminases increased (mild and reversible).

The following adverse reactions were not reported during the commercial use of ViATIM but were reported respectively following the use of the monovalent typhoid Vi polysaccharide vaccine and the monovalent inactivated hepatitis A vaccine:

Respiratory, thoracic and mediastinal disorders
Not known: aggravation of asthma.

General disorders and administration site conditions
Very rare: injection site nodule.

c. Paediatric Population
No data on the safety of ViATIM in children and adolescents below 16 years are available.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

4.9 Overdose

Cases of overdose have been reported with ViATIM where it was administered concomitantly with typhoid polysaccharide and/or hepatitis A vaccines. When adverse reactions were reported, they did not differ in nature from those described in section 4.8.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacterial and viral vaccines combined
ATC code: J07CA10 typhoid-hepatitis A

Four clinical studies provided useful data on immune responses to ViATIM. A total of 1090 subjects were included, with 179, 610, 243 and 58 subjects vaccinated in each study.

After the primary vaccination the seroprotection rate for HAV (% ≥ 20mIU/mL) ranged between 95.6% and 99.4% after 14 days and between 98.7% and 100% after 28 days.

The seroprotection rate for Vi (%≥1µg/mL) ranged between 83% and 89% after 14 days and between 69.8% and 91% after 28 days.

In one study that evaluated anti-Vi antigen seroprotection rates at years 1, 2 and 3 after the first dose of ViATIM and after re-vaccination with ViATIM at year 3, results were as follows:

	ViATIM			
	Year 1	Year 2	Year 3	28 days after Re-vaccination at Year 3
Number of vaccinees	139	124	112	46
% of vaccinees seroprotected (95% CI)	44.6 (36.2-53.3)	40.3 (31.6-49.5)	32.1 (23.6-41.6)	69.6 (54.2-82.3)

Serological data show continuing protection against hepatitis A for up to 36 months in subjects who responded to the first dose of ViATIM. Anti-HAV antigen seroprotection rates at years 1, 2 and 3 after the first dose of ViATIM and after re-vaccination with ViATIM at year 3 were as follows:

	ViATIM			
	Year 1	Year 2	Year 3	28 days after Re-vaccination at Year 3
Number of vaccinees	140	124	112	46
% ≥ 20 mIU/ml (95% CI)	99.3 (96.1-100)	98.4 (94.3-99.8)	99.1 (95.1-100)	100 (92.3-100)

Similar results were seen at all timepoints in the control group who received concomitant monovalent typhoid Vi polysaccharide and inactivated hepatitis A vaccines.

In an open randomised study, the immunogenicity of the concomitant administration of ViATIM with the combined, adsorbed, tetanus, low dose diphtheria and inactivated poliomyelitis vaccine (Td-IPV) at two separate sites was compared to the separate administration at different time points in healthy adults.

Seroconversion/seroprotection rates observed 28 days after vaccination in Per Protocol subjects were as follows:

	Group A (Concomitant administration)	Group B (Separate administration)
	N=161	N=154
Anti-HAV seroconversion rate (≥ 20 mIU/mL) n (%) [95% CI]	139 (100%)* [97.3; 100.0]	127 (100%)** [97.1; 100.0]
Anti-Vi seroconversion rate (≥ 4-fold rise) n (%) [95% CI]	134 (83.2%) [76.7; 88.2]	135 (87.7%) [81.5; 92.0]
Anti-D seroprotection rate (≥ 0.1 IU/mL) n (%) [95% CI]	158 (98.1%) [94.7; 99.4]	149 (96.8%) [92.6; 98.6]
Anti-T seroprotection rate (≥ 0.1 IU/mL) n (%) [95% CI]	161 (100%) [97.7; 100.0]	154 (100%) [97.6; 100.0]
Anti-Polio 1 {1/dil} seroprotection rate (≥ 5) n (%) [95% CI]	161 (100%) [97.7; 100.0]	154 (100%) [97.6; 100.0]
Anti-Polio 2 {1/dil} seroprotection rate (≥ 5) n (%) [95% CI]	161 (100%) [97.7; 100.0]	154 (100%) [97.6; 100.0]
Anti-Polio 3 {1/dil} seroprotection rate (≥ 5) n (%) [95% CI]	161 (100%) [97.7; 100.0]	154 (100%) [97.6; 100.0]

* N=139 (initially HAV seronegative subjects)
** N=127 (initially HAV seronegative subjects)

Non-inferiority of the concomitant administration of ViATIM and Td-IPV vaccines compared to the separate administration was demonstrated for all the valences, except for the Vi valence.

For the Vi valence, the seroprotection rates (anti-Vi titres ≥ 1 µg/mL) increased from 7.5% in Group A and 7.1% in Group B at Day 0 to 86.3% and 94.8% respectively, 28 days after vaccination. In initially non-protected individuals (anti-Vi titres < 1 µg/mL), seroconversion rates observed 28 days after vaccination were as follows:

	Group A (Concomitant administration)	Group B (Separate administration)
	N=149	N=143
Anti-Vi seroconversion rate (≥ 4-fold rise) n (%) [95% CI]	132 (88.6%) [82.5 , 92.8]	128 (89.5%) [83.4 , 93.5]

In initially non-protected individuals, the anti-Vi seroconversion rate (≥ 4-fold rise) for concomitant vaccines administration was non-inferior to the separate administration.

Paediatric Population
No data on the efficacy of ViATIM in children and adolescents below 16 years are available

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with this vaccine, or with the monovalent vaccines contained within this combined vaccine, reveal no special hazard for humans based on single, repeated dose and local tolerance toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactivated hepatitis A vaccine component:
2-Phenoxyethanol
Ethanol anhydrous
Formaldehyde
Medium 199 Hanks (without phenol red)* supplemented with polysorbate 80
*Medium 199 Hanks (without phenol red) is a complex mixture of amino acids (including phenylalanine), mineral salts (including potassium), vitamins and other components (including glucose), diluted in water for injections and pH adjusted with hydrochloric acid or sodium hydroxide

Typhoid Vi polysaccharide vaccine component:
Phosphate buffer solution:
Sodium chloride
Disodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other vaccines or 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.
Keep the vaccine in the outer carton in order to protect from light.

6.5 Nature and contents of container

Dual-chamber pre-filled syringe (type I glass): 0.5 ml of suspension in the chamber closest to the plunger and 0.5 ml of solution in the chamber closest to the needle, with a plunger-stopper (chlorobutyl and bromobutyl rubber elastomer blend), a tip cap (elastomer) and a by-pass stopper (elastomer).
Pack size of 1 or 10 pre-filled syringes supplied with or without needle.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The two vaccine components should only be mixed immediately prior to injection.
Shake before mixing and again prior to injection to obtain a homogeneous suspension. The contents of the two chambers are mixed by slowly advancing the plunger. The final volume to be injected is 1 millilitre.
The vaccine should be visually inspected before administration for any foreign particulate matter. The mixed vaccine is a cloudy, whitish suspension. The vaccine should not be used in case of unexpected particles in it.

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
Lyons
France

8 MARKETING AUTHORISATION NUMBER

PA2131/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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