NEW ZEALAND DATA SHEET

1 AVAXIM SUSPENSION FOR INJECTION

AVAXIM®, Suspension for injection

Hepatitis A virus.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Avaxim is a sterile suspension for injection containing formaldehyde-inactivated hepatitis A virus (GBM strain) adsorbed onto aluminium hydroxide.

Each 0.5mL dose contains:

Active ingredient:
Hepatitis A virus* inactivated by formaldehyde ……160 antigen units**

* GBM strain cultured on MRC-5 human diploid cells. MRC-5 is a cell line that was derived from human embryonic lung tissue in the 1960s.

** In the absence of an international standardised reference, the antigen content is expressed using an in-house reference.

Contains phenylalanine. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Suspension for injection

Avaxim is a cloudy, whitish suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Avaxim is indicated for active immunisation against hepatitis A infection in adults and children 2 years and over.

Vaccination against viral hepatitis A is recommended for individuals who are or will be at increased risk of infection:

- travellers to areas of moderate or high endemicity for hepatitis A
- visitors to rural and remote indigenous communities
- child day-care and pre-school personnel

- the intellectually disabled and their carers
- health care providers
- sewerage workers
- men who have sex with men
- injecting drug users
- patients with chronic liver disease
- haemophiliacs who may receive pooled plasma concentrates

4.2 DOSE AND METHOD OF ADMINISTRATION

The dose is 0.5 mL for each injection. The dose is the same for adults and children.

The primary vaccination is performed with one single dose of vaccine. The booster injection can be given 6 to 36 months after the primary vaccination.

Avaxim may be used as a booster in individuals previously vaccinated with another inactivated hepatitis A vaccine.

The combined purified Vi polysaccharide typhoid and inactivated hepatitis A vaccine (Vivaxim) may be given as a booster injection 6 to 36 months after primary vaccination with Avaxim, in individuals over 16 years travelling to areas where hepatitis A and typhoid are endemic.

Avaxim may be used as a booster injection 6 to 36 months after a primary vaccination performed by the combined purified Vi polysaccharide typhoid and inactivated hepatitis A vaccine (Vivaxim) to ensure long-term protection against infection with hepatitis A virus.

As the vaccine is adsorbed, it must be injected by the intramuscular route in order to minimise local reactions. The recommended injection site is the deltoid region.

Do not administer by intradermal or intravenous injection. Ensure that the needle does not enter a blood vessel.

Shake the prefilled syringe before injection to obtain a homogenous suspension.

This vaccine must not be mixed with other vaccines in the same syringe.

The prefilled syringe is for single use only and any residue must be discarded.

4.3 CONTRAINDICATIONS

Avaxim should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine (ie as defined in Section 2 Qualitative and quantitative composition) or after previous administration of the vaccine or vaccine containing the same components or constituents.

Vaccination must be postponed in case of febrile or acute disease.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As each dose contains formaldehyde, caution should be exercised when the vaccine is administered to individuals with hypersensitivity to this product.

As the vaccine may contain undetectable traces of neomycin, which is used during vaccine production, caution should be exercised when the vaccine is administered to individuals with hypersensitivity to this antibiotic (and other antibiotics of the same class).

This vaccine contains polysorbate which may cause local skin reactions.

As with other injectable vaccines, appropriate medical treatment and supervision should always be available in case of anaphylactic reactions. Adrenaline should always be readily available whenever the injection is given.

Immunogenicity of the vaccine could be impaired by immunosuppressive treatment or in immunodeficiency. In such cases, it is recommended to postpone the vaccination until the end of the treatment and/or the resolution of the disease. Nevertheless, vaccination of individuals with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited.

Because of the incubation period of the disease, infection may be present but not clinically apparent at the time of vaccination. In this case, the vaccination may have no effect on the development of hepatitis A.

The vaccine does not provide protection against infection caused by hepatitis B virus, hepatitis C virus, hepatitis E virus or by other liver pathogens.

As with any vaccine, vaccination with Avaxim may not protect 100% of susceptible individuals.

Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

As with all injectable vaccines, the vaccine must be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these individuals

In exceptional circumstances, the vaccine may be administered by the subcutaneous route in individuals suffering from thrombocytopenia or in individuals at risk of haemorrhage.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling injury and manage syncopal reactions.

Use in the Elderly

Immunogenicity and clinical experience with Avaxim in the elderly is limited.

Paediatric Use

Safety and effectiveness of Avaxim below the age of 2 years have not been established.

Effect on laboratory tests

Interference of Avaxim with laboratory tests has not been studied.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

For individuals requiring immediate and longer term protection, such as travellers departing on short notice to endemic areas or contacts of infected individuals requiring longer term post exposure prophylaxis, Avaxim may be administered concomitantly with immunoglobulin. The vaccine may be administered concurrently with immunoglobulin providing different injection sites are used. Seroconversion rates are unaffected although antibody titres may be lower than those obtained with vaccine alone.

Information on the concomitant use of Avaxim and other vaccines is limited. There is evidence for concurrent administration of Typhim Vi (typhoid Vi polysaccharide vaccine) or live yellow fever vaccine without any interference with the immune response.

Separate injection sites and separate syringes must be used in case of concomitant administration with other medicinal products.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Avaxim has not been evaluated for the effects on fertility.

Use in Pregnancy - Category B2

Animal reproduction studies have not been conducted with this vaccine. Data on the use of this vaccine in pregnant women are limited. Therefore, the administration of the vaccine during pregnancy is not recommended. Avaxim should be given to pregnant women only if clearly needed, and following an assessment of the risks and benefit.

Use in Lactation

It is not known whether this vaccine is excreted in human milk. Caution must be exercised when Avaxim 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.

4.8 UNDESIRABLE EFFECTS

Clinical Trial Experience

The adverse reactions reported during clinical trials were generally mild, short term and resolved without treatment.

Local reactions at the injection site

This was most frequently a local pain sometimes associated with erythema. The appearance of a nodule at the injection site was observed in very rare cases.

Systemic reactions

Mild fever, asthenia, headache, myalgia or arthralgia and gastrointestinal disorder were most frequently reported.

Mild reversible elevation of serum transaminase has been observed on rare occasions.

Reactions were less frequently reported after the booster injection than after the first dose.

In individuals seropositive against Hepatitis A virus, this vaccine was as well tolerated as in seronegative individuals.

Adults

The reactogenicity of Avaxim was assessed using the same methodology in all the clinical development trials undertaken, making it possible to consolidate the results. A total of 2,204 adults received at least one dose of the final formulation of Avaxim by the intra-muscular route.

Local reactions were observed in 13.2% of vaccine recipients after the first dose and 9.9% after the booster dose. General symptoms were reported in 27.3% of vaccine recipients after the first dose and 13.6% after the booster dose.

Two comparative studies compared the reactogenicity of Avaxim with a commercially available hepatitis A vaccine. The first study showed no statistical difference in the reactogenicity for seronegative patients. In the second study there was a significantly lower incidence of local reactions with Avaxim than with the comparator, both after the first and booster doses ($p<0.5$). This study was randomised but not blinded.

Table 1 - Summary of reactogenicity of Avaxim in adults after I.M. vaccination

Reaction	1st Dose No. = 2,204	Booster No. = 2,044
Local (any reaction)	**13.2%**	**9.9%**
Pain	11.7%	9.3%
Redness > 3cm	0.5%	0.5%
Haematoma > 3cm	1.0%	0.5%

Reaction	1st Dose No. = 2,204	Booster No. = 2,044
Other (pruritus etc.)	0.2%	0.3%
Systemic (any reaction)	**27.3%**	**13.6%**
Feverish feeling	5.2%	2.0%
Asthenia	13.5%	6.5%
Headache	9.7%	4.8%
Myalgia/arthralgia	10.3%	5.6%
GI disorder	6.1%	2.4%
Other (dizziness, discomfort,…..)	0.8%	0.4%

Children

In the combined clinical trials a total of 261 children received the first dose and 135 received the booster dose of Avaxim.

Table 2 - Local and systemic reactions reported in children within 7 days of vaccination

Reaction	1st Dose	Booster
Immediate (any reaction)	5/261 (1.9%)	4/135 (3.0%)
Pain	3/260 (1.2%)	0/135 (0%)
Redness	3/260 (1.2%)	2/135 (1.5%)
Headache	0/260 (0%)	2/135 (1.5%)
Local	31/260 (11.9%)	22/135 (16.3%)
Pain (crying)	16/260 (6.2%)	12/135 (8.9%)
Redness	18/260 (6.9%)	13/135 (9.6%)
Haematoma	1/260 (0.4%)	1/135 (0.7%)
Induration/oedema	1/260 (0.4%)	0/135(0%)
Systemic	16/260 (6.2%)	11/135(8.1%)
Fever (axillary ≥37.5° C)	6/260 (2.3%)	5/135 (3.7%)
Asthenia (drowsiness)	5/260 (1.9%)	3/135 (2.2%)
Headache	2/260 (0.8%)	3/135 (2.2%)
Myalgia/arthralgia	7/260 (2.6%)	2/135 (1.5%)
GIT upset	2/260 (0.8%)	1/135 (0.7%)
Behavioural change	3/260 (1.2%)	0/135 (0%)

Post-Marketing Experience

Based on spontaneous reporting, the following additional adverse events have been reported during the commercial use of Avaxim. These events have been very rarely (< 0.01 %) reported; however as exact incidence of rates cannot be calculated precisely, their frequency is qualified as ‘Not known’.

Nervous system disorders

- Headache, vasovagal syncope

Gastrointestinal disorders

- Nausea, diarrhoea, vomiting, abdominal pain

Skin and subcutaneous tissue disorder

- Urticaria, rashes associated or not with pruritus

Musculoskeletal and connective tissue disorders

- Arthralgia, myalgia

General disorders and administration site condition

- Injection site pain, injection site rash, injection site nodule, pyrexia, asthenia

Investigation

- Transaminases increased (mild and reversible)

Reporting of suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia). In New Zealand, any suspected adverse reactions should be reported at https://nzphvc.otago.ac.nz/reporting/

4.9 OVERDOSE

Cases of administration of more than the recommended dose (overdose) have been reported with Avaxim. The adverse events reported in these cases did not differ in nature to those described in Section 4.8 Undesirable effects.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or 0800 POISON (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

ATC code: J: ANTIINFECTIVES FOR SYSTEMIC USE; J07 (vaccines) B (Viral vaccines) C (Hepatitis vaccines) 02 (Hepatitis A, inactivated, whole virus)

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Hepatitis A is generally transmitted by the faecal-oral route through contaminated water or food. Blood and sexual (oral-anal relations) transmission has been demonstrated.

Avaxim confers immunity against hepatitis A virus by inducing antibodies. The measured antibody titres are greater than those obtained after passive immunisation with immunoglobulin. They are comparable to antibody titres obtained after vaccination with other inactivated hepatitis A vaccines with proven protective efficacy. The efficacy of this vaccine has not been demonstrated in field studies.

14 days after vaccination more than 90% of immunocompetent individuals are protected. One month after the first injection 100% of individuals are protected. Immunity persists for at least 36 months and is reinforced after a booster injection.

Primary immunisation should be given at least two weeks prior to anticipated exposure to the hepatitis A virus.

Data relative to long-term persistence of Hepatitis A virus antibodies (anti-HAV) following vaccination with Avaxim are not currently available. Based on antibody kinetic modelling, it is predicted that anti-HAV antibody would persist for at least 10 years after the completion of the two dose vaccination schedule.

Clinical trials

The efficacy of Avaxim has been determined by the comparison of the antibody titres produced by Avaxim with that of a control Hepatitis A vaccine that had previously been demonstrated to confer protective efficacy in a controlled trial of healthy children in Thailand. Seroprotection was defined as anti-HAV >20mLU/mL. The protective effect of Avaxim against infection with Hepatitis A has not been assessed. In total 4,220 subjects received Avaxim in 9 studies in adults and 3 studies in children during the course of the clinical development program.

The pivotal studies were two multicentre, open, randomised controlled studies. In the first 840 adults were enrolled 420 who received Avaxim and 420 who received the control Hepatitis A vaccine. In the second study 423 adults were enrolled 212 who were inoculated with Avaxim and 211 who received the control vaccine.

In the first pivotal study Avaxim immunogenicity was assessed at 8 weeks after the primary injection (in the subjects that were HAV seronegative (<20 mLU/mL) at inclusion) with 99.3% of subjects achieving seropositive titres (95% CI 97.5- 99.9%). The Geometric Mean Titre (GMT) was 138.4 mLU/mL (95%CI 124.5-153.9). The seroconversion rate 4 weeks post the last dose (week 28) was 100% (95%CI 99.0-100) with GMT of 4,189.6 mLU/mL (95%CI 3,792.3-4,628.6 mLU/mL). Additional analyses were made one, two and three years post-booster. All subjects tested were still seropositive.

Table 3 - Immunogenicity 1, 2 and 3 years post-booster

	1 year post Booster	2 years post Booster	3 years post booster
Number of subjects.	264	229	169
Titre	50-20832	49-13184	59-6928
GMT (Geometric Mean Titre)	1556	1077	872
95%CI	1361-1779	939-1234	754-1010

Percent Positive	100%	100%	100%
95%CI	98.6-100%	98.4-100%	97.8-100%

In the second pivotal study 100% of subjects were seropositive 8 weeks after the primary injection (95%CI 97.7-100%) with the GMT being 114mLU/mL (95%CI 102-127). Four weeks after the booster injection the GMT had risen to 3,557mLU/mL (95%CI 2,985-4,239).

Three studies have determined the immunogenicity of Avaxim in children aged between 2 and 17 years. Study 1 was conducted in haemophiliac males in France, with the other two studies being conducted in school children in Venezuela and Taiwan. Seroprotection was defined as >20mLU/mL.

Table 4 - Immunogenicity in Children

Study	Group	No.*	Week 2		Week 4		Week 24		Week 28	
			%SC	GMT	%SC	GMT	%SC	GMT	%SC	GMT
France	3-12	26	nd	Nd	100 (89-100)	838 (615-1142)	100 (89-100)	288 (229-364)	100 (89-100)	5896 (4669-74460)
Venezuela	4-9	57/56	100 (94-100)	79 (68-90)	Nd	nd	100 (93-100)	268 (222-323)	100 (93-100)	8613 (7358-10084)
Venezuela	9-15	64/62	100 (94-100)	69 (61-79)	Nd	nd	100 (93.8-100)	212 (173-258)	100 (94-100)	5832 (4667-7287)
Venezuela	4-15	121/118	100 (97-100)	74 (67-81)	Nd	nd	100 (97-100)	236 (206-271)	100 (97-100)	6999 (6070-8071)
Taiwan	2-5	50/48	nd	nd	100 (93-100)	107 (92-125)				
Taiwan	6-17	70/68	nd	nd	100 (95-100)	162 (136-193)				
Taiwan	2-17	120/116	nd	nd	100 (97-100)	136 (120-154)				

*number enrolled/initially seronegative

Long-term persistence of vaccine-induced anti-HAV was evaluated in a study designed to determine the antibody (anti-HAV and anti-Vi) persistence 1, 2 and 3 years after primary dose of the combined purified Vi polysaccharide typhoid and inactivated hepatitis A vaccine (Vivaxim ®) or of the simultaneous individual vaccines [purified Vi polysaccharide vaccine (Typhim Vi™) and inactivated hepatitis A vaccine (Avaxim)]. This study was an open label, randomised trial which included 360 adult subjects; 179 in the Vivaxim group and 181 in the Avaxim and Typhim Vi group (Table 5).

Table 5 - Hepatitis A antibody persistence at year 1, year 2 and year 3 after primary vaccination with either Vivaxim or Avaxim and Typhim Vi

Anti-HAV	Vivaxim			Avaxim and Typhim Vi		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Number of Subjects	140	124	112	139	116	103

Anti-HAV	Vivaxim			Avaxim and Typhim Vi		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
GMT (Geometric Mean Titre)	548	419	425	321	257	258
95% CI	443-678	340-518	345-524	265-390	204-324	202-329
Seroprotection Rate (≥ 20 mLU/mL)	99.3	98.4	99.1	99.3	98.3	99.0
95% CI	96.1-100	94.3-99.8	95.1-100	96.1-100	93.9-99.8	94.7-100

At year 3, a subset of the original subjects underwent re-vaccination with the combined vaccine (Vivaxim) and the antibody response was recorded 28 days later (Table 6).

Table 6 - Hepatitis A antibody persistence at year 3 before re-vaccination and 28 days after re-vaccination with Vivaxim

Anti-HAV	Vivaxim		Avaxim and Typhim Vi	
	Y3	Y3 + 28 days	Y3	Y3 + 28 days
Number of Subjects	46	46	37	37
GMT(Geometric Mean Titre)	451	15063	305	14273
95% CI	312-653	11742-19323	190-489	10957-18592
Seroprotection Rate (≥ 20 mLU/mL)	97.8	100	100	100
95% CI	88.5-99.9	92.3-100	90.5-100	90.5-100

Three years after primary vaccination with Avaxim, the hepatitis A seroprotection rate (percent ≥ 20 mLU/mL) was 99%. Three years after primary vaccination with Avaxim, the seroprotection rate for hepatitis A increased to 100% 28 days after a booster vaccination with Vivaxim, demonstrating anamnestic immune response against hepatitis A.

Non-inferior immunogenicity of Avaxim when used as a booster following the primary dose of Vivaxim was demonstrated in a study designed to demonstrate that either of the two hepatitis A vaccines (Avaxim and VAQTA®) could be used as a booster following primary vaccination with Vivaxim. This study was an open label, randomised trial which included 120 adult subjects. The results showed that one month after the booster injection, the immunogenicity elicited by vaccination with Vivaxim and booster Avaxim was non-inferior to that of Avaxim and booster Avaxim in terms of GMT of anti-HAV antibody; and similarly that the immunogenicity elicited by vaccination with Vivaxim and booster VAQTA was non-inferior to that of Avaxim and booster Avaxim (Table 7).

Table 7 - Anti-HAV titres one month after booster without adjustment on age (GMT at Month 7, HAV seronegative subjects)

	Avaxim and Avaxim	Vivaxim and Avaxim	Vivaxim and VAQTA
Number of Subjects	34	36	28
GMT (Geometric Mean Titre)	3283	4515.3	3528
95% CI	2318.4-4648.9	3301.8-6174.7	2638.8-4716.8

5.2 PHARMACOKINETIC PROPERTIES

No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Avaxim has not been evaluated for the genotoxic potential.

Carcinogenicity

Avaxim has not been evaluated for the carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 0.5mL dose contains:

Other components:

Aluminium hydroxide hydrate (quantity expressed as aluminium)	…….0.3 mg
Phenoxyethanol (preservative)	….……2.5 microlitres
Formaldehyde (preservative)	…….12.5 micrograms
Medium 199 (Hanks)***	……..…...up to 0.5 mL

*** Medium 199 Hanks (without phenol red) is a complex mixture of amino acids, mineral salts, vitamins, and other substances, diluted in water for injection, supplemented with polysorbate 80 and with a pH adjusted with hydrochloric acid or sodium hydroxide.

Neomycin (≤ 2.5 µg) and bovine serum albumin (< 50 nanograms) may be present as residual traces.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

6.2 INCOMPATIBILITIES

This vaccine must not be mixed with other vaccines or medicinal products.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2° to 8°C (REFRIGERATE. DO NOT FREEZE).

6.5 NATURE AND CONTENTS OF CONTAINER

Single dose prefilled syringe, 0.5 mL.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Australia:
sanofi-aventis australia pty ltd
Talavera Corporate Centre – Building D
12 – 24 Talavera Road
Macquarie Park NSW 2113
Australia
Tel: 1800 818 806

New Zealand:
sanofi-aventis new zealand limited
Level 8, 56 Cawley St
Ellerslie
Auckland
New Zealand
Tel: 0800 283 684

9 DATE OF FIRST APPROVAL

01 March 2001

10 DATE OF REVISION OF THE TEXT

27 February 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Movement of text to align with the data sheet explanatory guide
1; 4.8; 5; 6.1; 8	Editorial changes
3; 4.7; 5.2; 6.2; 6.3; 6.6; 9	Section added
4.5	Revised warning for concomitant administration