VIVAXIM®

Salmonella typhi Vi polysaccharide and inactivated hepatitis A virus vaccine

NAME OF THE MEDICINAL PRODUCT

Salmonella typhi Vi polysaccharide and inactivated hepatitis A virus antigen vaccine.

DESCRIPTION

VIVAXIM® contains a sterile suspension of purified *Salmonella typhi* Vi polysaccharide and formaldehyde inactivated hepatitis A virus antigen (GBM strain) adsorbed onto aluminium hydroxide. VIVAXIM® is presented in a dual-chamber by-pass syringe. The contents of both chambers are mixed immediately prior to injection by slowly pressing the plunger.

Each 1 millilitre dose of mixed vaccine contains:

Active Ingredients:

Salmonella typhi Vi polysaccharide (Ty 2 strain)	25 µg
Hepatitis A virus antigen*	160 ELISA 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.

Other Components:

Salmonella typhi Vi polysaccharide typhoid vaccine components:

Phosphate buffer solution containing:	
Sodium chloride	4.150 mg
Sodium phosphate – dibasic dihydrate	0.065 mg
Sodium phosphate – monobasic	0.023 mg
Water for injections	up to 0.5 ml

Inactivated hepatitis A virus vaccine components:

Aluminium hydroxide (quantity expressed as aluminium)	0.3 mg
Phenoxyethanol (preservative)	2.5 µL
Formaldehyde (preservative)	12.5 µg

Medium 199 (Hanks)*	up to 0.5 mL

* Supplemented with polysorbate 80. Medium 199 (Hanks) without phenol red, is a complex mixture of amino acids including phenylalanine, mineral salts, vitamins and other components such as glucose, diluted in water for injections.

Neomycin (≤ 2.5 µg) and Bovine serum albumin (< 10 Nanograms) may be present as residual traces.

Hydrochloric acid or sodium hydroxide for adjustment of pH.

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.

PHARMACOLOGICAL PROPERTIES

A minimum of fourteen days after vaccination is necessary to allow development of an adequate immune response prior to a potential exposure.

Typhoid fever seroprotecion threshold is not known and estimates vary between 0.6μg/mL and 1.5μg/mL. Seroprotecion level of ≥ 1μg/mL has been used in the studies supporting immunogenicity of VIVAXIM®. There is a consensus on the 4-fold increase as a criterion for seroconversion and this is used in all clinical trials.

By consensus hepatitis A seroprotection level is ≥ 20 mIU/mL.

The efficacy of the combined vaccine has not been demonstrated in field studies.

Clinical Trials

The combined vaccine, VIVAXIM®, produced immune responses for primary vaccination and for booster vaccination that were non-inferior to those of the two monovalent vaccines TYPHIM Vi™ and AVAXIM™.

Study 1

The immunogenicity and safety of VIVAXIM® have been determined by this pivotal study designed to compare the immunogenicity of salmonella typhi Vi and hepatitis A antigens administered either together, using a dual chamber syringe (VIVAXIM®), or separately at two different sites (TYPHIM Vi™ and AVAXIM™ vaccines). The study was open label and randomised and included 360 adult subjects; 179 in the VIVAXIM® group and 181 in the TYPHIM Vi™ + AVAXIM™ group.

Forty subjects, 17 in the VIVAXIM® group and 32 in the separately administered vaccine group were found to be seropositive at inclusion and were excluded from the analysis of immunogenicity. Consequently the per-protocol population evaluated 28 days after vaccination consisted of:

VIVAXIM® – 172 subjects in the typhoid Vi analysis, and 157 for the hepatitis A analysis
TYPHIM Vi™ and AVAXIM™ – 173 in the typhoid Vi analysis, and 149 in the hepatitis A analysis.

Twenty eight days after the VIVAXIM® injection, the anti-typhoid Vi seroconversion rate (≥ four-fold rise in titre) was 84.7% and the anti-hepatitis A seroprotection rate (≥ 20 mIU/mL) was 98.7%. (Table 1 and 2)

Study 1 Follow-Up

A follow-up study examined residual antibody levels 3 years after the primary vaccination. At this time, a subset of the original subjects underwent re-vaccination with the combined vaccine; antibody response was recorded 28 days later.

Three years after primary vaccination with VIVAXIM®, the typhoid Vi seroprotection rate (percent ≥1μg/mL) was 32.1%. One month following revaccination with VIVAXIM® the seroprotection rate for typhoid Vi increased to 69.6%; the seroconversion rate for typhoid Vi was 26.1%.

Three years after primary vaccination with VIVAXIM® the hepatitis A seroprotection rate (percent ≥20mIU/mL) was 99.1%. The seroprotection rate for hepatitis A increased to 100% 28 days after re-vaccination.

Results of the follow-up study are shown in tables 3 and 4.

Study 2

The batch consistency of VIVAXIM® was demonstrated in a multicentric double-blind randomised study of adult subjects, using 3 batches of the combined vaccine. The seroconversion rate for typhoid antibody was 92.1% and for hepatitis A antibody was 100% (Tables 1 and 2)

Combined Studies 1 and 2

The two studies combined included a total of 789 subjects. The combined seroconversion rate for anti-Vi antibody was 90.3% and seroprotection rate for anti-HAV antibody was 99.7%. (Tables 1, 2)

Study 3

A single centre, open, randomised study of adult subjects, demonstrated non-inferiority of the hepatitis booster response of the combined vaccine VIVAXIM® compared with the single component inactivated hepatitis A vaccine, AVAXIM™. The primary vaccination of all subjects was AVAXIM™. Six months after initial vaccination subjects underwent booster vaccination and antibody levels were measured 28 days later. (Table 5)

Table 1 – Combined studies 1 and 2

Anti-typhoid Vi antibody response after vaccination with VIVAXIM®

	14 days after vaccination				28 days after vaccination			
Study	Number of subjects	Seroconversion[1] (%) [95%CI[2]]	Seroprotection[3] (%) [95%CI]	GMT [95% CI]	Number of subjects	Seroconversion (%) [95% CI]	Seroprotection (%)[95% CI]	GMT [95% CI]
1	177	86.4% [80.5 - 91.1]	89.3% [83.7- 93.4]	2.98 [2.61- 3.39]	176	84.7% [78.5 - 89.6]	85.2% [79.1 - 90.1]	2.64 [2.31 - 3.02]
2	-	-	-	-	609	92.1% [89.7 - 94.1]	90.6% [88.0 - 92.8]	2.89 [2.71 - 3.09]
All	177	86.4% [80.5 - 91.1]	89.3% [83.7 - 93.4]	2.98 [2.61 - 3.40]	785	90.3% [88.0 - 92.3]	89.4% [87.1 - 91.5]	2.83 [2.67 - 3.01]

1. Seroconversion – four fold rise in antibody titres
2. CI – confidence interval
3. Seroprotection - ≥ 1 μg/mL

Table 2 – Combined studies 1 and 2

Hepatitis A antibody response after vaccination with VIVAXIM®[1]

	14 days after vaccination			28 days after vaccination		
Study	Number of subjects	Seroprotection[2] (%) [95%CI[3]]	GMT [95%CI]	Number of subjects	Seroprotection (%)[95% CI]	GMT [95% CI]
1	160	95.6% [91.2 – 98.2]	235 [191 – 290]	159	98.7% [95.5 – 99.8]	783 [654 – 938]
2	-	-	-	581	100% [99.4 – 100]	882 [817 – 951]
All	160	95.6% [91.2 – 98.2]	235 [191 – 290]	740	99.7% [99.0 – 100]	858 [799 – 921]

1. In previously seronegative subjects
2. Seroprotection - ≥ 20mIU/mL
3. CI – confidence interval

Table 3: Study 1 – Follow-up

Typhoid antibody persistence and response to re-vaccination with VIVAXIM®

	Year 1	Year 2	Year 3	Year 3 +28 days[1]
Number of subjects	139	124	112	46
GMT[2]	0.850	0.698	0.641	1.52
95% CI	0.716 – 1.01	0.585 – 0.834	0.530 – 0.776	1.12 – 2.06
Percent seroprotected[3]	44.6	40.3	32.1	69.6
95% CI	36.2 – 53.3	31.6 – 49.5	23.6 – 41.6	54.2 – 82.3

1. 28 days after re-vaccination
2. GMT – Geometric Mean Titre
3. greater than or equal to 1 μg/mL

Table 4: Study 1 – Follow-up

Hepatitis A antibody persistence and response to re-vaccination with VIVAXIM®

	Year 1	Year 2	Year 3	Year 3 +28 days[1]
Number of subjects	140	124	112	46
GMT[2]	548	419	425	15,063
95% CI	443 - 678	340 - 518	345 - 524	11,742 – 19,323
Percent seroprotected[3]	99.3	98.4	99.1	100
95% CI	96.1 - 100	94.3 – 99.8	95.1 - 100	92.3 - 100

1. 28 days after re-vaccination
2. GMT – Geometric Mean Titre
3. greater than or equal to 20 mIU/mL

Table 5: Study 3

Hepatitis A antibody responses to primary and booster vaccination

	Combined typhoid and hepatitis A vaccine VIVAXIM®			Inactivated hepatitis A vaccine AVAXIM™		
	Day 0	6 months	7 months	Day 0	6 months	7 months
Subject numbers	53	53	53	55	55	55
GMT[1]	10.5	219	4,576	10.7	194	3,760
Seroprotection rate (≥20mIU/mL)	0	100	100	0	100	100

95%CI	0 – 6.7	93.3 – 100	93.3 - 100	0 – 6.5	93.5 – 100	93.5 - 100

1. GMT – Geometric Mean Titre

INDICATIONS

VIVAXIM® is indicated for simultaneous active immunisation against typhoid fever and hepatitis A virus infections in subjects aged 16 and older.

CONTRAINDICATIONS

Usual contraindications to any immunisation.

Vaccination should be delayed in subjects with an acute severe febrile illness.

Known hypersensitivity to any constituent of VIVAXIM®.

PRECAUTIONS FOR USE

VIVAXIM® may contain residual traces of neomycin. Caution is advised in subjects with a known hypersensitivity to neomycin. If administered to these subjects, the vaccine should be given under close medical supervision.

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 the administration of the vaccine. Anaphylactoid reactions have been observed after vaccination with TYPHIM Vi™ (See ADVERSE REACTIONS).

VIVAXIM® should be administered at least 14 days prior to risk of exposure with *Salmonella typhi* and hepatitis A virus.

Do not administer VIVAXIM® by intravascular injection. Make sure that the needle does not penetrate a blood vessel.

VIVAXIM® should not be administered into the buttocks due to the varying amount of fatty tissue in this region. VIVAXIM® should be administrated by intramuscular route only, except in patients with thrombocytopenia or bleeding disorders where it may be administered by subcutaneous route.

Subcutaneous administration of VIVAXIM® may increase the risk of local adverse reaction.

Immunogenicity of VIVAXIM® 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 pathology allows the induction of an antibody response, even if limited.

Because of the long incubation period of hepatitis A, infection may be present but not clinically apparent at the time of vaccination. It is not known whether VIVAXIM® will prevent hepatitis A in such cases.

A single dose of VIVAXIM® does not ensure long-term protection against infection with hepatitis A virus. For long term protection a booster dose of inactivated hepatitis A virus vaccine is required 6 to 36 months after vaccination with VIVAXIM®.

VIVAXIM® does not protect against infection caused by other known liver pathogens including hepatitis B, hepatitis C and hepatitis E viruses.

VIVAXIM® does not protect against infection caused by *Salmonella enterica* other than serotype typhi.

This vaccine is to be used in subjects from the age of 16 and older. No clinical data on younger subjects is available.

Product is for single use in one patient only. Discard any residue.

Use In Children

There is no experience in use of Vivaxim in children aged <16 years.

Carcinogenicity, Mutagenicity, Impairment Of Fertility

VIVAXIM® has not been evaluated for carcinogenicity, mutagenicity, or impairment of fertility.

Use In Pregnancy – Category B2

VIVAXIM® is not recommended for pregnant women, particularly during the first trimester. The effect of VIVAXIM® on embryo-foetal development has not been assessed. However, as for any purified polysaccharide vaccine and inactivated viral vaccine, no risk to the foetus is to be expected.

VIVAXIM® should only be used in pregnant women after careful consideration of the risk-benefit ratio.

Use In Lactation

There are no data on the effect of the administration of VIVAXIM® during lactation. VIVAXIM® is therefore not recommended during lactation.

VIVAXIM® should only be used in lactating women after careful consideration of the risk-benefit ratio.

Interactions With Other Drugs

VIVAXIM® is a combination of purified Vi polysaccharide typhoid vaccine and inactivated hepatitis A vaccine. Therefore, concomitant administration with other inactivated vaccines using different syringes and at different injection sites may be performed and is unlikely to interfere with the immune response.

Based on data obtained from the concomitant administration of the monovalent vaccines (purified Vi polysaccharide typhoid vaccine and inactivated hepatitis A vaccine) with yellow fever vaccine, no interference with the immune response is expected when VIVAXIM® is administered concomitantly at a different site with yellow fever vaccine.

However no specific study has been carried out with VIVAXIM®.

Effects On Laboratory Tests

Not documented.

ADVERSE REACTIONS

Clinical Trial Experience

In controlled clinical studies, the most commonly reported reactions were those occurring at the injection site.

Pain at the injection site was reported by 89.9% of subjects following administration of VIVAXIM® compared with 83.2% of subjects who received monovalent Vi polysaccharide typhoid vaccine and inactivated hepatitis A vaccine concomitantly at separate injection sites.

Local reactogenicity: the following data show the risk of severe local reactions (or > 5cm) or reactions lasting more than 72 hours.

Table 6: Local reactions (severe or >72 hours) in the 7 days following vaccination

	HA/Vi ***N=787***	
	n (subjects)	%
AT LEAST ONE LOCAL EVENT	***719***	***91.4***
Pain	***710***	***90.2***
Severe Pain	34	4.3
Pain > 72 h	167	21.2
Erythema	***124***	***15.8***
Erythema > 5 cm	8	1.0
Erythema > 72 h	23	2.9
Induration/Oedema	***254***	***32.3***
Induration/Oedema > 5 cm	52	6.6
Induration/Oedema > 72 h	53	6.7
Ecchymosis	***26***	***3.3***
Ecchymosis. > 5 cm	1	0.1
Ecchymosis > 72 h	11	1.4

The reactions observed were as follows:

Nervous system disorders

Uncommon (0.1 - 1%): dizziness
Very common (>10%): headache

Gastrointestinal disorders

Common (1-10%): nausea; diarrhoea.

Skin and subcutaneous tissue disorders

Uncommon (0.1 - 1%): pruritus; rash.

Musculoskeletal, connective tissue and bone disorders

Common (1 - 10%): myalgia; arthralgia.

General disorders and administration site conditions

Very common (>10%): pain, induration/oedema, and erythema at the injection site; asthenia.

Common (1 - 10%): malaise; fever.

Post-Marketing Experience

Data gathered from Post-marketing surveillance for each monovalent vaccine**:**

These frequencies are based on spontaneous reporting rates and have been calculated using number of reports and estimated number of patients.

Gastrointestinal disorders

Very rare (<0.01%): vomiting, abdominal pain.

Immune system disorders

Very rare (<0.01%): anaphylactic reactions; serum sickness.

Respiratory, thoracic and mediastinal disorders

Very rare (<0.01%): asthma.

Skin and subcutaneous tissue disorders

Very rare (<0.01%): injection site inflammation; urticaria.

Investigation

Very rare (<0.01%): transaminases increased.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 millilitre of the mixed vaccine. VIVAXIM® should be administered by slow intramuscular injection in the deltoid region. VIVAXIM® must not be administered intradermally or intravenously.

Primary immunisation is achieved with a single dose of VIVAXIM®.

The vaccine should be administered at least 14 days prior to risk of exposure to both typhoid fever and hepatitis A.

A single dose of VIVAXIM® does not ensure long-term protection against infection with hepatitis A virus. For long-term protection a booster injection of inactivated hepatitis A vaccine is required 6 to 36 months later. It has been demonstrated that HAV antibodies persist for many years (at least 10 years) after the booster.

Revaccination against typhoid fever should be carried out with a single dose of purified Vi polysaccharide typhoid vaccine every 3 years in subjects who remain at risk.

The HA component of VIVAXIM® produces an adequate booster response when VIVAXIM® is given 6-36 months after primary vaccination with either inactivated hepatitis A vaccine or 36 months after primary vaccination with VIVAXIM®.

The two vaccine components must only be mixed immediately prior to injection. The contents of the two compartments are mixed by slowly advancing the plunger.

Shake before injection to obtain a homogeneous suspension. The mixed vaccine is a whitish opalescent suspension.

Contains no antimicrobial agent.

Each dual chamber syringe is for single use in a single patient only. Discard any residue.

All parenteral drugs and vaccine products should be inspected visually prior to administration for discolouration or particulate matter. In the event of either being observed, discard the vaccine.

OVERDOSAGE

There is no data on overdose of VIVAXIM®.

PRESENTATION

VIVAXIM® is contained in a type I glass, dual chamber, by-pass syringe (1 millilitre) with an elastomer (chlorobromobutyl) plunger stopper, elastomer (chlorobromobutyl) tip cap and elastomer (chlorobromobutyl) by-pass stopper.

The purified Vi polysaccharide typhoid vaccine (solution for injection) is contained in the chamber of the syringe closest to the needle, and the inactivated hepatitis A vaccine (suspension for injection) in the chamber closest to the plunger.

The typhoid polysaccharide component is a clear and colourless solution, the hepatitis A component (inactivated, adsorbed) is a cloudy whitish suspension.

STORAGE

Store in a refrigerator (2°C to 8°C)
Do not freeze. Do not use if the vaccine has been frozen.
The shelf-life is 36 months.
The expiry date is indicated on the label and packaging.

MANUFACTURER

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MEDICINE CLASSIFICATION

Prescription Medicine

DATE OF PREPARATION

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