

PRODUCT MONOGRAPH

HAVRIX

hepatitis A vaccine, inactivated

Suspension for injection

Active immunizing agent
against infection by hepatitis A virus

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4

Date of approval:
September 11, 2018

Submission Control No: 217904

© 2018 GSK group of companies or its licensor.
Trademarks are owned by or licensed to the GSK group of companies.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
DESCRIPTION.....	3
INDICATIONS AND CLINICAL USE.....	4
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	5
DRUG INTERACTIONS	7
DOSAGE AND ADMINISTRATION.....	7
OVERDOSAGE	10
ACTION AND CLINICAL PHARMACOLOGY	10
STORAGE AND STABILITY.....	11
DOSAGE FORMS, COMPOSITION AND PACKAGING	12
PART II: SCIENTIFIC INFORMATION.....	14
PHARMACEUTICAL INFORMATION.....	14
CLINICAL TRIALS.....	14
DETAILED PHARMACOLOGY	17
MICROBIOLOGY	17
TOXICOLOGY	17
REFERENCES	18
PART III: CONSUMER INFORMATION.....	22

HAVRIX

Hepatitis A vaccine, inactivated

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intramuscular Injection	Sterile suspension for injection/ HAVRIX 1440 contains: 1440 ELISA units per 1 mL of formaldehyde-inactivated hepatitis A virus (HM175 hepatitis A virus strain); HAVRIX 720 Junior contains: 720 ELISA units per 0.5 mL of formaldehyde-inactivated hepatitis A virus (HM175 hepatitis A virus strain).	Aluminium (as aluminium hydroxide), amino acids for injection, disodium phosphate, monopotassium phosphate, polysorbate 20, potassium chloride, sodium chloride, water for injection. Residue*: neomycin sulphate

*From the manufacturing process

DESCRIPTION

HAVRIX (hepatitis A vaccine, inactivated) is a sterile suspension containing formaldehyde-inactivated hepatitis A virus (HM175 hepatitis A virus strain) adsorbed onto aluminium hydroxide.

INDICATIONS AND CLINICAL USE

HAVRIX (hepatitis A vaccine, inactivated) is indicated for active immunization against disease caused by hepatitis A virus (HAV). HAVRIX is approved for use in persons 12 months of age and older. Primary immunization should be administered at least 2 weeks prior to anticipated exposure to HAV.

Please refer to the National Advisory Committee on Immunization (NACI) and the Canadian Immunization Guide for recommendations of use.

CONTRAINDICATIONS

HAVRIX (hepatitis A vaccine, inactivated) should not be administered:

- to subjects with known hypersensitivity to any component of the vaccine preparation or component of the container, or to subjects having shown signs of hypersensitivity after previous HAVRIX administration. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

As with other vaccines, the administration of HAVRIX should be postponed in subjects with severe febrile illness. The presence of a minor infection however, is not a contraindication.

WARNINGS AND PRECAUTIONS

General

As with other injectable vaccines, appropriate medication (e.g. adrenaline) should be readily available for immediate use in case of anaphylaxis or anaphylactoid reactions following administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunization.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Hematologic

HAVRIX (hepatitis A vaccine, inactivated) should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

Immune

It is possible that subjects may be in the incubation period of hepatitis A infection at the time of immunization. It is not known whether HAVRIX will prevent hepatitis A in such cases.

Since there is a possibility that the vaccine may contain trace amounts of neomycin, the possibility of an allergic reaction in individuals sensitive to this substance should be kept in mind when considering the use of this vaccine (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

As with other vaccines, subjects with an impaired immune system may not obtain adequate antibody titres after the primary immunization course. Such patients may require administration of additional doses of HAVRIX. However, no specific dosing recommendations can be made at this time.

Renal

As with other vaccines, hemodialysis patients may not obtain adequate antibody titres after the primary immunization course. Such patients may require administration of additional doses of HAVRIX. However, no specific dosing recommendations can be made at this time.

Special Populations

Pregnant Women:

Animal reproduction studies and adequate human data on use during pregnancy are not available. However, as with all inactivated viral vaccines, the risks to the fetus are considered to be negligible. HAVRIX should be used during pregnancy only when clearly needed.

Nursing Women:

Animal reproduction studies and adequate human data on use during lactation are not available. Therefore, caution should be exercised if HAVRIX is to be administered to breast feeding women.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety profile presented below is based on data from more than 5,300 subjects.

Frequency of doses	Adverse Event	System/Organ Class
Very Common: ≥ 10%	Irritability	Psychiatric disorders
	Headache	Nervous system disorders
	Pain and redness at the injection site, fatigue	General disorders and administration site conditions
Common: ≥ 1% and < 10%	Appetite loss	Metabolism and nutrition disorders
	Drowsiness	Nervous system disorders
	Gastrointestinal symptoms (such as nausea, vomiting, diarrhea)	Gastrointestinal disorders
	Malaise, injection site reaction (such as swelling or induration), fever (≥ 37.5°C)	General disorders and administration site conditions
Uncommon: ≥ 0.1% and < 1%	Upper respiratory tract infection, rhinitis	Infections and infestations
	Dizziness	Nervous system disorders
	Rash	Skin and subcutaneous tissue disorders
	Myalgia, musculoskeletal stiffness	Musculoskeletal and connective tissue disorders
	Influenza-like illness	General disorders and administration site conditions
Rare: ≥ 0.01% and < 0.1%	Hypoaesthesia, paraesthesia	Nervous system disorders
	Pruritus	Skin and subcutaneous tissue disorders
	Chills	General disorders and administration site conditions

Administration of HAVRIX with measles-mumps-rubella (MMR) and varicella (V) vaccines

In a co-administration study (HAV 231) evaluating immune response in toddlers receiving HAVRIX 720 Junior (N=324) or HAVRIX 720 Junior plus measles-mumps-rubella (MMR) plus varicella vaccines (N=462) or MMR plus varicella plus HAVRIX 720 Junior (N=455), the primary analysis of safety (N=1,241) demonstrated that all the three vaccines, HAVRIX, MMR and varicella, whether co-administered or administered alone, were well tolerated. Reactogenicity and safety of HAVRIX when co-administered with MMR/V vaccines is consistent with the known safety profile of HAVRIX.

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported with HAVRIX.

Immune system disorders	Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness
Nervous system disorders	Convulsions
Vascular disorders	Vasculitis
Skin and subcutaneous tissue disorders	Angioneurotic oedema, urticaria, erythema multiforme
Musculoskeletal and connective tissue disorders	Arthralgia

DRUG INTERACTIONS

Overview

Since HAVRIX is an inactivated vaccine, its concomitant use with other inactivated vaccines is unlikely to result in interference with immune responses. When concomitant administration of other vaccines is considered necessary, the vaccines must be given with different syringes and at different injection sites.

Clinical experiences with the concomitant administration of HAVRIX and the recombinant hepatitis B virus vaccine, ENGERIX-B, has been satisfactory. No interference in the respective immune responses to both antigens has been observed.

HAVRIX can be given concomitantly with any of the following vaccines: typhoid, yellow fever, cholera (injectable), tetanus, or with monovalent and combination vaccines comprised of measles, mumps, rubella and varicella. See also Clinical Trials section.

HAVRIX must not be mixed with other vaccines.

Drug-Drug Interactions

The concomitant administration of HAVRIX (hepatitis A vaccine, inactivated) and immune globulin (human) does not influence the seroconversion rate, but may result in a relatively lower anti-HAV antibody titre than when the vaccine is given alone. HAVRIX and immune globulin (human) should be administered at separate injection sites.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Primary Immunization

Adults from 19 years onwards

A single dose of HAVRIX 1440 (hepatitis A vaccine, inactivated) (1 mL suspension) is used for primary immunization.

Children and adolescents from 1 year up to and including 18 years of age

A single dose of HAVRIX 720 Junior (0.5 mL suspension) is used for primary immunization. If a pediatric vial is not available, a pediatric dose of 0.5 mL may be withdrawn from the HAVRIX 1440 vial.

Booster Dose

A booster dose is recommended at any time between 6 and 12 months after a single dose of HAVRIX 1440 or HAVRIX 720 Junior in order to ensure long-term protection.

Long-term persistence of serum antibodies to hepatitis A virus after vaccination with HAVRIX is under evaluation. Nevertheless, data available after 5 years show persistence of antibodies which is consistent with a projected 20 years persistence (based on mathematical calculations).

Concomitant administration with immune globulin (human)

Concomitant administration of HAVRIX and immune globulin (human) may be considered when a subject is at risk of being exposed to hepatitis A before adequate anti-HAV antibody titres can be reached.

Administration

HAVRIX should be injected **intramuscularly** in the deltoid region in adults and children, in the antero-lateral part of the thigh in young children up to 2 years of age. The vaccine **should not** be administered intramuscularly in the gluteal region or subcutaneously/intradermally since administration by these routes may result in a less than optimal anti-HAV antibody response.

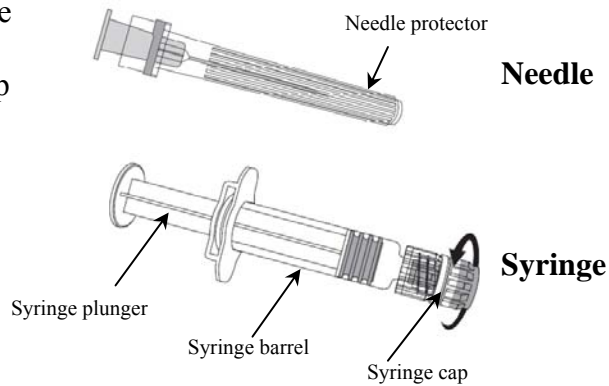
As with all parenterals, vaccine products should be inspected visually for any foreign particulate matter and/or discolouration prior to administration. Before use of HAVRIX, the vial/syringe should be well shaken to obtain a slightly opaque, white suspension. Discard the vaccine if the contents of the vial/syringe appear otherwise.

The vaccine must be used as supplied.

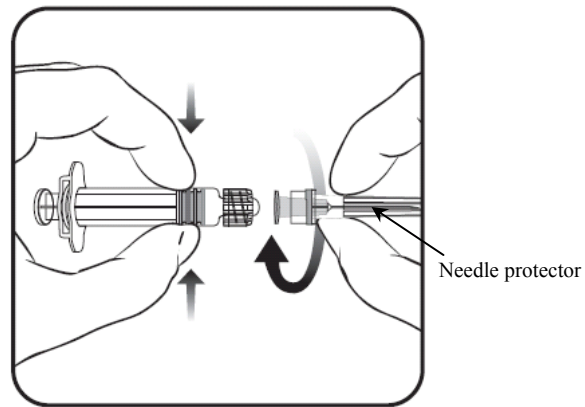
Syringe Instructions

To attach the needle to the syringe, refer to the drawing below

1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.



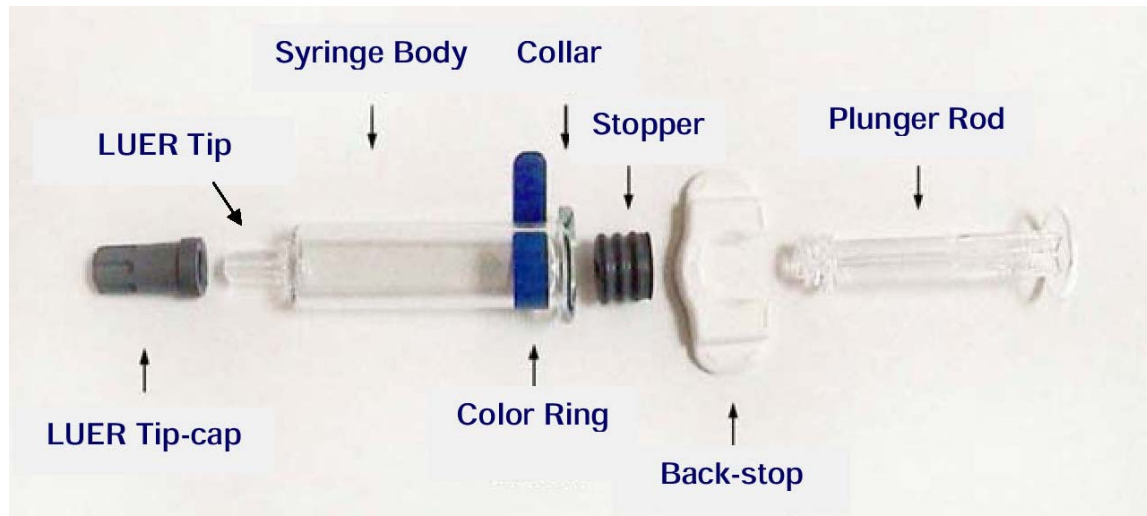
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see drawing).



3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

Note: The syringe provided with HAVRIX might be slightly different (without screw thread) than the syringe in the above drawing. In that case, the needle should be attached following the below instructions.

Do not remove the white back-stop from the syringe. Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger clockwise until slight resistance is felt. **Do not** over tighten. Remove syringe LUER Tip-cap and needle cap. Attach needle by pressing and twisting in a clockwise rotation until secured to the syringe.



HAVRIX should never be administered intravenously.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Cases of overdose have been reported during post-marketing surveillance. Adverse events reported following overdose were similar to those reported with normal vaccine administration.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

HAVRIX (hepatitis A vaccine, inactivated) confers immunity against hepatitis A virus (HAV) infection by inducing the production of specific anti-HAV antibodies.

Immune response

In clinical studies involving subjects of 18 – 50 years of age, specific humoral antibodies against HAV were detected in more than 88% of vaccinees at day 15 and 99% at month 1 following administration of a single dose of HAVRIX 1440 (hepatitis A vaccine, inactivated).

In clinical studies involving subjects of 1 – 18 years of age, specific humoral antibodies against HAV were detected in more than 93% of vaccinees at day 15 and 99% of vaccinees one month following administration of HAVRIX 720 Junior.

The mean titre of anti-HAV antibodies induced by HAVRIX is at least 3 times higher than the maximum observed after passive immunization using immune globulin (human). In a randomly selected subset of subjects, vaccine induced anti-HAV antibodies were

shown to be qualitatively indistinguishable from immune globulin (human) anti-HAV antibodies.

To obtain long-term immunity a booster dose is recommended at any time between 6 and 12 months after primary vaccination with HAVRIX 1440 Adult or HAVRIX 720 Junior, to induce long-term antibody titres.

Long-term persistence of serum antibodies to hepatitis A virus after vaccination with HAVRIX is under evaluation. Nevertheless, data available after 5 years show persistence of antibodies which is consistent with a projected 20 years persistence (based on mathematical calculations).

Primates exposed to the virulent heterologous hepatitis A strain were vaccinated 2 days after exposure. This post exposure vaccination resulted in total protection of the animals.

Efficacy of HAVRIX for outbreak control

Results of hepatitis A outbreak control program showed a substantial drop in symptomatic cases in 4,930 vaccinees within 3 weeks of receiving 1 dose of hepatitis A vaccine. In villages where more than 70% of estimated susceptible individuals were vaccinated, a dramatic drop in the number of symptomatic cases of disease was observed within 8 weeks of vaccination.

Immunization Recommendations (see also Canadian Immunization Guide)

Active immunization with HAVRIX is indicated for the following individuals: Armed Forces personnel who travel to higher endemicity areas or to areas where hygiene is poor have an increased risk of HAV infection, close contacts of infected persons since virus shedding of infected persons may occur for a prolonged period, individuals with chronic liver disease or who are at risk of developing chronic liver disease such as hepatitis B (HB) and hepatitis C (HC) chronic carriers and alcohol abusers and susceptible individuals in areas of intermediate to high prevalence of hepatitis A.

Immunization with HAVRIX is particularly recommended in subjects who are, or will be, at increased risk of infection such as: travellers (i.e., to areas where the prevalence of hepatitis A is high), persons for whom hepatitis A is an occupational hazard (i.e., employees in day-care centres, nursing, medical and paramedical personnel in hospitals and institutions, especially gastroenterology and pediatric units, sewage workers, and food handlers), persons for whom there is an increased risk of transmission of Hepatitis A (i.e., homosexuals, persons with multiple sexual partners, abusers of injectable drugs, hemophiliac patients), specific population groups known to have higher incidence of Hepatitis A (i.e., North American Indians, Inuits, recognized community-wide HAV epidemics).

STORAGE AND STABILITY

The vaccine should not be used beyond the expiry date stamped on the vial or syringe.

Store HAVRIX (hepatitis A vaccine, inactivated) in the original package in order to protect from light. The vaccine must be stored at 2 to 8°C.

Do not freeze; discard if vaccine has been frozen.

Stability data indicate that HAVRIX is stable at temperatures up to 25°C for 3 days. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

HAVRIX (hepatitis A vaccine, inactivated) is available as HAVRIX 1440 (1440 ELISA Units/mL) and HAVRIX 720 Junior (720 ELISA Units/0.5 mL) suspension for injection.

Composition

HAVRIX is a sterile suspension containing formaldehyde-inactivated hepatitis A virus (HM175 hepatitis A virus strain) adsorbed onto aluminium hydroxide.

The virus is propagated in MRC₅ human diploid cells. Before viral extraction, the cells are extensively washed to remove culture medium constituents. A virus suspension is then obtained by lysis of the cells followed by purification using ultrafiltration techniques and gel chromatography. Inactivation of the virus is assured by treatment with formalin. The viral antigen content of HAVRIX is determined by an ELISA test. Each dose is standardized to ensure a viral antigen content of not less than:

	ELISA Units	Dose Volume
HAVRIX 1440	1440	1 mL
HAVRIX 720 Junior	720	0.5 mL

The virus is adsorbed on aluminium (0.5 mg/1 mL adult dose, 0.25 mg/0.5 mL pediatric dose) in the form of aluminium hydroxide. Excipients: aluminium (as aluminium hydroxide), amino acids for injection, disodium phosphate, monopotassium phosphate, polysorbate 20, potassium chloride, sodium chloride, water for injection. Residue from the manufacturing process: neomycin sulphate (less than 10 ng for HAVRIX 720 Junior; less than 20 ng for HAVRIX 1440).

HAVRIX meets the World Health Organization requirement for biological substances including those for final vaccine residual bovine serum albumin.

Packaging

HAVRIX 1440:

Single Dose 1 mL Vials: In packages of 1, 10* or 25* vials.

Single Dose 1 mL Prefilled Syringes: In packages of 1 prefilled syringe.

HAVRIX 720 Junior:

Single Dose 0.5 mL Vials: In packages of 1 or 10* vials.

Single Dose 0.5 mL Prefilled Syringes: In packages of 1 prefilled syringe.

*Format not available in Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: hepatitis A vaccine, inactivated

Product Characteristics

HAVRIX (hepatitis A vaccine, inactivated) is a sterile suspension containing formaldehyde-inactivated hepatitis A virus (HM175 hepatitis A virus strain) adsorbed onto aluminium hydroxide.

CLINICAL TRIALS

Clinical studies have been conducted in Asia, Europe, Latin America, USA and Canada to evaluate the immunogenicity and reactogenicity of HAVRIX.

Summary of Study Demographics, Trial Design and Efficacy Results

Study No.	Trial design	Dosage and route of administration	No. of subjects	Patient Demographics	Immunogenicity Results ¹	
					SC Rate (%)	GMT (mIU/ml)
HAV-104	Double-blind, randomized, multi-country, multi-centre	Intramuscular injection (into deltoid region) 1440 EL.U/1 mL dose 0, 6 month dosing schedule	Enrolled: 150	Healthy adults aged 18 to 50 years	97.6 ²	577 ²
HAV-107	Double-blind, randomized, multi-country, multi-centre	Intramuscular injection (into deltoid region) 1440 EL.U/1 mL dose 0, 6 month dosing schedule	Enrolled: 150	Healthy adults aged 18 to 40 years	99.3 ²	490 ²
HAV-112	Double-blind, randomized, multi-country, multi-centre	Intramuscular injection (into deltoid region) 1440 EL.U/1 mL dose 0, 12 month dosing schedule	Enrolled: 194	Healthy adults aged 21 to 40 years	99.4 ³	387 ³

Study No.	Trial design	Dosage and route of administration	No. of subjects	Patient Demographics	Immunogenicity Results ¹	
					SC Rate (%)	GMT (mIU/ml)
HAV-115	Open randomized, multi-country, multi-centre	Intramuscular injection (into deltoid region) Group 1: 720 EL.U/0.5 mL dose Group 2: 1440 EL.U/1 mL dose 0, 6 month dosing schedule	Enrolled : 202	Healthy adolescents aged 12 to 19 years	Group 1: 99.0 Group 2: 100	Group 1: 249 Group 2: 349
HAV-117B	Open study, multi-country, multi-centre	Intramuscular injection (into deltoid region) 720 EL.U/0.5 mL dose 0, 6 month dosing schedule	Enrolled : 60	Healthy children aged 2 to 13 years	100	305
HAV-118	Open prospective study, multi-country, multi-centre	Intramuscular injection (into deltoid region, and sometimes the thigh muscle) 720 EL.U/0.5 mL dose 0, 12 month dosing schedule	Enrolled : 54	Healthy children aged 2 to 11 years	95.5	184
HAV-122	Open randomized study, multi-country, multi-centre	Intramuscular injection (into deltoid region) 720 EL.U/0.5 mL dose 0, 6 month dosing schedule	Enrolled: 81	Healthy children aged 2 to 15 years	96.8	194
HAV-129	Open study, multi-country, multi-centre	Intramuscular injection (into deltoid region) 720 EL.U/0.5 mL dose 0, 6 month dosing schedule	Enrolled: 120	Healthy adolescents aged 9 to 18 years	100	256
Alaskan Outbreak Control Programme	Independent study, multi-country, multi-centre	Children/teenagers received dose level of 720 EL.U/0.5 mL Adults received dose level of 1440 EL.U/1 mL	Enrolled: 4,930	Mean age (\pm standard deviation): 16.47 \pm 14.9 years Male: 51% Female: 49%	92 ⁴	Children / teenagers: 269 ⁵ Adults: 254 ⁶
HAV-231	Open randomized study, USA, multi-centre	Toddlers 15 months of age Group 1: HAVRIX 720 EL.U/0.5 mL dose 0, 6 month dosing schedule Group 2: HAVRIX 720 EL.U/0.5 mL + MMR + varicella vaccines 0, 6-9 month dosing schedule Group 3: MMR + varicella vaccines + HAVRIX 720 EL.U/0.5 mL	Enrolled: 1474	Mean age (\pm standard deviation): 15 months \pm 0.21 months Male: 53%. Female: 47%	Group 1: 99 Group 2: 99.7 Group 3: 100 (SC rates post-dose 2) ⁷	Group 1: 1390 Group 2: 1895 Group 3: 1770 (GMCs post-dose 2) ⁸

Study No.	Trial design	Dosage and route of administration	No. of subjects	Patient Demographics	Immunogenicity Results ¹	
					SC Rate (%)	GMT (mIU/ml)
		0, day 42 (1 st dose HAVRIX 720 EL.U/0.5 mL), month 7.5-10.5 (2 nd dose HAVRIX 720 EL.U/0.5 mL)				

1. Results at 1 month after initial dose
2. Average of 3 lots
3. Average of 2 lots
4. Results at 3-4 weeks after initial dose
5. Average for 3 different age groups (1-2 years, 3-9 years and 10-19 years)
6. 20-40 years age group
7. Seroconversion rates for anti-HAV antibodies
8. GMCs for anti-HAV antibodies

Efficacy

Clinical studies performed in Europe (HAV 104, 107, 112) evaluated immune response in adults to primary vaccination with HAVRIX 1440. Antibodies were measured at screening, day 15, and at month 1 and 6.

In an overall analysis of immunogenicity following vaccination the seroconversion rate was 98.9% at month 1 and the Geometric Mean Titre was 466 mIU/mL.

Clinical studies performed in Asia, Europe, Latin America, and Alaska (HAV 115, 117B, 118, 122, 129 and Alaskan outbreak program) evaluated immune response in subjects between 2 and 18 years receiving 720 EL.U.

The overall analysis of immunogenicity following vaccination showed that the seroconversion rate was 99.3% at month 1 and the Geometric Mean Titre was 253 mIU/mL.

Administration of HAVRIX with measles-mumps-rubella (MMR) and varicella (V) vaccines

A co-administration study (HAV 231) evaluated immune response in toddlers receiving HAVRIX 720 Junior (group 1) or HAVRIX 720 Junior + MMR + V vaccines (group 2) or MMR + V + HAVRIX 720 Junior (group 3). Study HAV 231 demonstrated non-inferiority of anti-HAV immune response 31 days after the 2nd dose of HAVRIX when the 1st dose had been co-administered with MMR + V compared to HAVRIX alone (1st co-primary objective). HAV 231 also demonstrated non-inferiority of the MMR + V immune responses 42 days after the first dose of MMR co-administered with varicella and HAVRIX vaccines compared to MMR + V alone (2nd co-primary objective). All antigens in study HAV 231, including anti-measles, anti-rubella and anti-varicella antibodies, had similar immune responses in the co-administration group (HAV+MMR+V) and control groups (HAV Group and the MMR+V – HAV group). Thus, co-administration of HAVRIX with MMR and varicella vaccines does not impact the immunogenicity of either of these vaccines.

Safety

For safety information please refer to the Adverse Reactions Section, Part I.

DETAILED PHARMACOLOGY

Not applicable.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Not applicable.

REFERENCES

1. Atkins M, Zambon M, Watkins P. Hepatitis A virus infection. Should susceptible homosexual men be offered immunization. *BMJ*. 1993;307(6903):562.
2. Chriske H, Abdo R, Richrath R, Braumann S. Hepatitis-A-Infektionsgefährdung bei Kanal- und Klärwerksarbeitern [The Risk of Hepatitis-A Infection among Sewer Workers]. *Arbeitsmed*. 1990;25(6):285-287.
3. CIG, 2016. Canadian Immunization Guide, accessed March 29, 2017 <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-6-hepatitis-a-vaccine.html>.
4. Cossar JH, Reid D, Fallon RJ, Bell EJ, Riding MH, Follett EA et al. A cumulative review of studies on travellers, their experience of illness and the implications of these findings. *J Infect*. 1990;21(1):27-42.
5. Coutinho RA, Albrecht-van Lent P, Lelie N, Nagelkerke N, Kuipers H, Rijdsdijk T. Prevalence and incidence of hepatitis A among male homosexuals. *Br Med J (Clin Res Ed)*. 1983;287(6407):1743-1745.
6. D'Hondt E, Purcell RH, Emerson SU, Wong DC, Shapiro M, Govindarajan S. Efficacy of an inactivated hepatitis A vaccine in pre- and postexposure conditions in marmosets. *J Infect Dis*. 1995;171 Suppl 1:S40-S43.
7. Desenclos JC, MacLafferty L. Community wide outbreak of hepatitis A linked to children in day care centres and with increased transmission in young adult men in Florida 1988-9. *J Epidemiol Community Health*. 1993;47(4):269-273.
8. Frölich J, Zeller I. Hepatitis-A-Infektionsrisiko bei den Mitarbeitern einer grossen Kläranlagenbetreibergesellschaft. *Arbeitsmed*. 1993;28(11):503-505.
9. Germanaud J, Causse X, Barthez JP. Prevalence of antibodies to hepatitis A virus in health care workers. *Eur J Clin Microbiol Infect Dis*. 1993;12(7):572-573.
10. Gerritzen A, Schneeweis KE, Brackmann HH, Oldenburg J, Hanfland P, Gerlich WH et al. Acute hepatitis A in haemophiliacs. *Lancet*. 1992;340(8829):1231-1232.
11. Hadler SC, Erben JJ, Francis DP, Webster HM, Maynard JE. Risk factors for hepatitis A in day-care centers. *J Infect Dis*. 1982;145(2):255-261.
12. Hanna J. Hepatitis A in a Child Day-care Centre. *Commun Dis Intell*. 1993;17(4):73-75.

13. Harkess J, Gildon B, Istre GR. Outbreaks of hepatitis A among illicit drug users, Oklahoma, 1984-87. *Am J Public Health*. 1989;79(4):463-466.
14. Hepatitis A among drug abusers. *MMWR Morb Mortal Wkly Rep*. 1988;37(19):297-300, 305.
15. Hesla PE. Hepatitis A in Norwegian troops. *Vaccine*. 1992;10 Suppl 1:S80-S81.
16. Hofmann F, Berthold H, Wehrle G. Immunity to hepatitis A in hospital personnel. *Eur J Clin Microbiol Infect Dis*. 1992;11(12):1195.
17. Hoke CH, Jr., Binn LN, Egan JE, DeFraitess RF, MacArthy PO, Innis BL et al. Hepatitis A in the US Army: epidemiology and vaccine development. *Vaccine*. 1992;10 Suppl 1:S75-S79.
18. Holter E, Siebke JC. Hepatitis A in young Norwegian drug addicts and prison inmates. *Infection*. 1988;16(2):91-94.
19. Keeffe EB. Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? *Am J Gastroenterol*. 1995;90(2):201-205.
20. Koster D, Hofmann F, Berthold H. Hepatitis A immunity in food-handling occupations. *Eur J Clin Microbiol Infect Dis*. 1990;9(4):304-305.
21. Kruppenbacker J, Bock H, Bienzle U. Immunogenicity, Safety and Interference of SB Biologicals' Inactivated hepatitis A vaccine with other simultaneously administered travel vaccinations: experience of multicenter trial in Germany. Presented, Fourth International Conference on Travel Medicine. 1995.
22. Mannucci PM. Outbreak of hepatitis A among Italian patients with haemophilia. *Lancet*. 1992;339(8796):819.
23. Mannucci PM, Gdovin S, Gringeri A, Colombo M, Mele A, Schinaia N et al. Transmission of hepatitis A to patients with hemophilia by factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. The Italian Collaborative Group. *Ann Intern Med*. 1994;120(1):1-7.
24. McFarlane ES, Embil JA, Manuel FR, Thieboux HJ. Antibodies to hepatitis A antigen in relation to the number of lifetime sexual partners in patients attending an STD clinic. *Br J Vener Dis*. 1981;57(1):58-61.
25. NACI, 2016. National Advisory Committee on Immunization (NACI) Update on the Recommended use of Hepatitis A Vaccine. 2016. Published by the Public Health Agency of Canada. Accessed March 29, 2017. <https://www.canada.ca/en/public-health/services/publications/healthy-living/update-recommended-use-hepatitis-vaccine.html>.

26. Rothschild C, Pol S, Mattlinger B, Reijasse D, Torchet MF, Gazengel C. Vaccination against Hepatitis A Virus in French Hemophilic Children. *Vox Sanguinis*. 1995;69(1):80-81.
27. Rubertone MV, DeFraités RF, Krauss MR, Brandt CA. An outbreak of hepatitis A during a military field training exercise. *Mil Med*. 1993;158(1):37-41.
28. Sjogren MH, Tanno H, Fay O, Sileoni S, Cohen BD, Burke DS et al. Hepatitis A virus in stool during clinical relapse. *Ann Intern Med*. 1987;106(2):221-226.
29. Steffen R. Risk of hepatitis A in travellers. *Vaccine*. 1992;10 Suppl 1:S69-S72.
30. Steffen R. Hepatitis A and hepatitis B: risks compared with other vaccine preventable diseases and immunization recommendations. *Vaccine*. 1993;11(5):518-520.
31. Stewart T, Crofts N. An outbreak of hepatitis A among homosexual men in Melbourne. *Med J Aust*. 1993;158(8):519-521.
32. Totos G, Gizaris V, Papaevangelou G. Hepatitis A vaccine: persistence of antibodies 5 years after the first vaccination. *Vaccine*. 1997;15(11):1252-1253.
33. Van Damme P, Mathei C, Thoelen S, Meheus A, Safary A, Andre FE. Single dose inactivated hepatitis A vaccine: rationale and clinical assessment of the safety and immunogenicity. *J Med Virol*. 1994;44(4):435-441.
34. Van Damme P, Thoelen S, Cramm M, De Groote K, Safary A, Meheus A. Inactivated hepatitis A vaccine: reactogenicity, immunogenicity, and long-term antibody persistence. *J Med Virol*. 1994;44(4):446-451.
35. Van Damme P, Thoelen S, Van der Auwera JC Baré, Meheus A. Viral hepatitis among health care workers - epidemiology and prevention. In 1993;(International Congress on Occupational Health):133-137.
36. Van Damme P, Thoelen S Meheus. Long-term immunogenicity of an inactivated hepatitis A vaccine. IX Triennial International Symposium on Viral Hepatitis and Liver Disease. 1996;21-25.
37. Van Damme P, Van Herck K, Thoelen S Meheus. Long-term immunogenicity of an inactivated hepatitis A vaccine. 5th International Conference on Travel Medicine 1997;24-27.
38. Vernon AA, Schable C, Francis D. A large outbreak of hepatitis A in a day-care center: association with non-toilet-trained children and persistence of IgM antibody to hepatitis A virus. *Am J Epidemiol*. 1982;115(3):325-331.

39. WHO. Prevention of foodborne hepatitis A – Considerations on the vaccination of food handlers. WHO Tech Rep Ser. 1993;68:25-26.

PART III: CONSUMER INFORMATION**HAVRIX**

hepatitis A vaccine, inactivated

This leaflet is part III of a three-part "Product Monograph" published for HAVRIX (hepatitis A vaccine, inactivated) approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HAVRIX. Contact your doctor or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE**What the vaccine is used for:**

HAVRIX is a vaccine used to prevent hepatitis A disease. Vaccination is the best way to protect against this disease.

HAVRIX is approved for use in persons 12 months of age and older. The first dose of the vaccine should be given at least 2 weeks prior to anticipated exposure to hepatitis A disease.

What it does:

The vaccine works by causing the body to produce its own protection (antibodies) against hepatitis A disease.

When it should not be used:

HAVRIX should not be used:

- if you or your child have a known allergy to any component of the vaccine (see What the important medicinal ingredient is and What the important nonmedicinal ingredients are sections).
- if you or your child have shown signs of a serious allergic reaction after a previous dose of this vaccine or any vaccine intended to protect against hepatitis A infection. Signs of an allergic reaction may include skin rash, shortness of breath and swelling of the face or tongue.

Immunization should be postponed if you or your child has a severe fever or infection.

What the medicinal ingredient is:

The medicinal ingredient in HAVRIX is inactivated hepatitis A virus. None of the components of the vaccine are infectious.

What the nonmedicinal ingredients are:

Aluminium (as aluminium hydroxide), amino acids for injection, disodium phosphate, monopotassium phosphate, polysorbate 20, potassium chloride, sodium chloride and water for injection. Residue from the manufacturing process: neomycin sulphate.

What dosage forms it comes in:

HAVRIX is presented as a suspension for injection.

WARNINGS AND PRECAUTIONS

BEFORE you use HAVRIX talk to your doctor or pharmacist if:

- you or your child has a severe infection with a high temperature (over 38°C).
- you or your child have any known allergies.
- you or your child is on dialysis for kidney disease.
- you or your child have a poor immune system due to illness or drug treatment.
- you are pregnant or breastfeeding.
- you or your child have a bleeding problem or bruise easily.

Please tell your doctor if you are taking or have recently taken any other medicines. You can be given other vaccines at the same time as HAVRIX, however these vaccines will be given at different injection sites.

Fainting can occur following, or even before, any needle injection; therefore, tell the doctor or nurse if you or your child fainted with a previous injection.

INTERACTIONS WITH THIS VACCINE

HAVRIX and immune globulin (human) should be administered at separate injection sites.

When administration of other vaccines with HAVRIX is considered necessary, the vaccines must be given with different syringes and at different injection sites.

PROPER USE OF THIS VACCINE

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Usual dose:

HAVRIX is injected into the muscle in your upper arm or in the front of the thigh in young children.

Primary Immunization:

The first dose of the vaccine should protect you or your child with normal immunity from infection with hepatitis A virus within 2-4 weeks after the injection.

Booster Dose:

To ensure that you or your child is protected long-term you or your child should have a second (booster) dose of the vaccine 6 to 12 months after the first injection.

Missed Dose:

If you or your child misses a scheduled injection, talk to your doctor to arrange another visit.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all vaccines, HAVRIX can have side effects.

Side effects that may occur are the following:

Very common (more than 10% of doses):

- Irritability.
- Headache.
- Pain and redness at the injection site, fatigue.

Common (between 1% and 10% of doses):

- Loss of appetite.
- Drowsiness.
- Diarrhea, nausea, vomiting.
- Swelling or hard lump at the injection site.
- Generally feeling unwell, fever.

Uncommon (between 0.1% and 1% of doses):

- Upper respiratory tract infection, runny or blocked nose.
- Dizziness.
- Rash.
- Aching muscles, muscular stiffness not caused by exercise.
- Flu-like symptoms, such as high temperature, sore throat, runny nose, cough and chills.

If any of the side effects get serious or if you notice any side effects not mentioned above, please tell your doctor.

This is not a complete list of side effects. For any unexpected effects while taking HAVRIX, contact your doctor or pharmacist.

HOW TO STORE IT

HAVRIX must be stored in a refrigerator between 2 and 8°C. **Do not freeze.** Discard if the vaccine has been frozen.

Do not use after expiration date shown on the label. The date for last use corresponds to the last day of the month mentioned.

Store all vaccines out of the reach and sight of children.

Store in the original package in order to protect from light.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:

If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:

Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 866-844-0018
 By toll-free fax: 866-844-5931
 By email: caefi@phac-aspc.gc.ca
 At the following website:
<http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>

By regular mail:
 The Public Health Agency of Canada
 Vaccine Safety Section
 130 Colonnade Road
 Ottawa, Ontario
 K1A 0K9 Address Locator 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.gsk.ca>

or by contacting the sponsor,

GlaxoSmithKline Inc.

7333 Mississauga Road

Mississauga, Ontario

L5N 6L4

1-800-387-7374

This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: July 3, 2018

© 2018 GSK group of companies or its licensor

Trademarks are owned by or licensed to the GSK group of companies.