BLK-MAX
Super Speciality Hospital

HEPATITIS A VACCINE

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- **Editor of Ten Books Child and its Health both in English and Hindi**
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- **Cricket Statistician for All India Radio ,Delhi Doordarshan, Radio Australia.**

Changing scenario of Hepatitis A disease in India

Which vaccine to choose for pro-protection?*

Amongst the available Inactivated vaccine

*Pro: word adapted from professional, expert or someone who has a lot of experience

PM-IN-HAV-PPT-240004, DoP March 2023

Disclaimer

- ✓*I am not a GSK employee*
- ✓*I will receive honoraria from GSK for this scientific meeting*

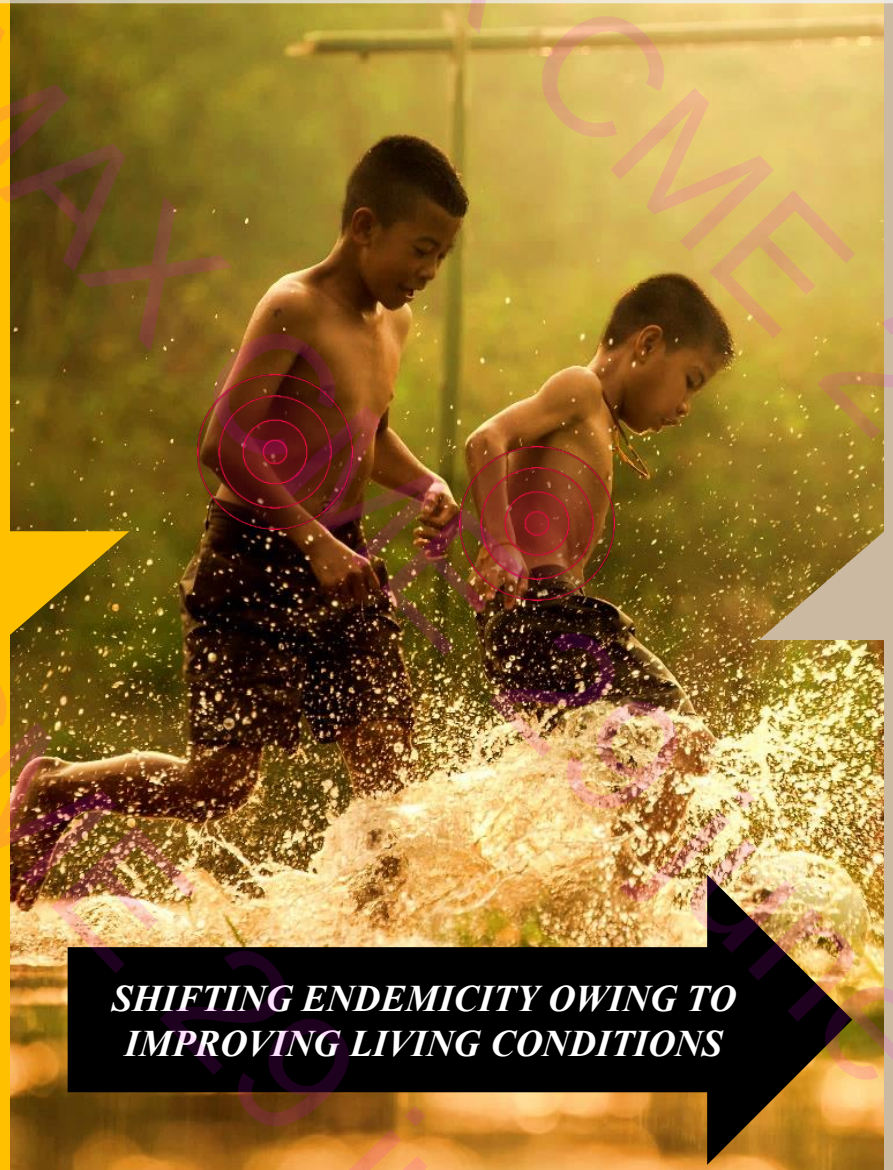
Evolution of Hepatitis A disease over time

Hepatitis A disease before 2000's

'THE PRE-VACCINE ERA'

- ✓ *In India, majority of the population acquired hepatitis A infection early in life, such that large proportion of population is immune to HAV*[1]
- ✓ *The disease was self-limiting & asymptomatic amongst children which played an important role in sustaining Transmission & immunity*[1]
- ✓ *Hepatitis A occurred in cycles, every 10–15 years, with majority of cases reported among children (≤15 years)*[1]

INCREASED BURDEN IN YOUNGER CHILDREN



Hepatitis A disease currently

'THE VACCINE ERA'

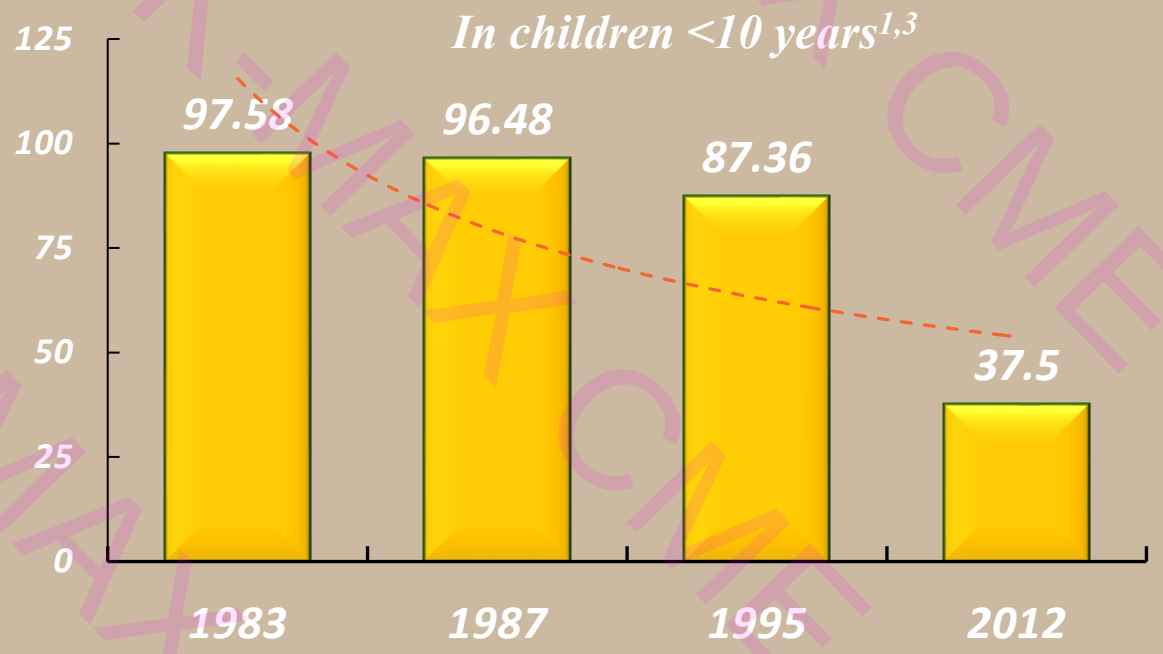
- ✓ *Recent reports suggest decreasing sero-prevalence across the country is increasing incidence of infection among adults and adolescents*[1]
- ✓ *The shift in age group, which acquires hepatitis A, towards adolescents and adults has amplified the incidence of symptomatic disease(frank hepatitis), since childhood HAV infection is usually asymptomatic* [1]

INCREASED BURDEN IN ADOLESCENTS & ADULTS

1. Chakravarti A, Bharara T. Epidemiology of Hepatitis A: Past and Current Trends [Internet]. Hepatitis A and Other Associated Hepatobiliary Diseases. IntechOpen; 2020.

Hepatitis A in India: Changing endemicity

Significant decrease in anti-HAV positivity across different studies in Indian children



Improved sanitation and water supplies are leading to reduced Hepatitis A endemicity in India[1,2]

2 out 3 children <10 years are vulnerable to Hepatitis A infection[1]

1. Arankalle V et al. Vaccine: Development and Therapy, 2014, 4: 7-13; 2. Agrawal A et al. Infect Dis Ther (2019) 8:483–497, 3. Chitambar SD et al. Southeast Asian J Trop Med Public Health. 1999 Jun;30(2):273-6;

Hepatitis A disease severity

Age wise severity

✓*Signs and symptoms of illness are more common among adults than among children, and the disease tends to be more severe in older age groups*[1]

≤6 years

- ✓ ***70%** asymptomatic,*[2]
- ✓ ***10%** develop jaundice*[1]

≥6 years

- ✓ *Typical asymptomatic,*[2]
- ✓ ***>70%** develop jaundice*[1]

Hospitalization severity

✓*Hospitalization rates were Significantly higher in adults & adolescent than in children.*[1]

- ✓ ***24%** hospitalization rate for <15 years old*[1]
- ✓ ***45%** hospitalization rate for >15 years old*[1]

- ✓ *Average hospitalization was for **7.6 days***[4]
- ✓ *About **20-180 days** of work loss/rest*[4]
- ✓ *Total household out of pocket expenditure for one HAV patient was around **25K***[4]

1. World Health Organization. Hepatitis A Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/hepatitis-a. Updated July 20, 2023. Accessed July 26, 2023; 2. Nelson NP, et al. MMWR Recomm Rep. 2020;69(5):1-38; 3.Agrawal A, Singh S, Kolhapure S, Hoet B, Arankalle V, Mitra M. Increasing Burden of Hepatitis A in Adolescents and Adults and the Need for Long-Term Protection: A Review from the Indian Subcontinent. Infect Dis Ther. 2019 Dec;8(4):483-49. 4.Rakesh PS et al. Indian J Med Res Indian J Med Res. 2017;146:426-429.

Hepatitis A outbreaks are becoming a major public concern

*According to the IDSP report in India, overall Hepatitis outbreaks reported in 2021 accounted for **110** cases, whereas for the years 2022-2023*, total reported cases increased to **977**.[1]*

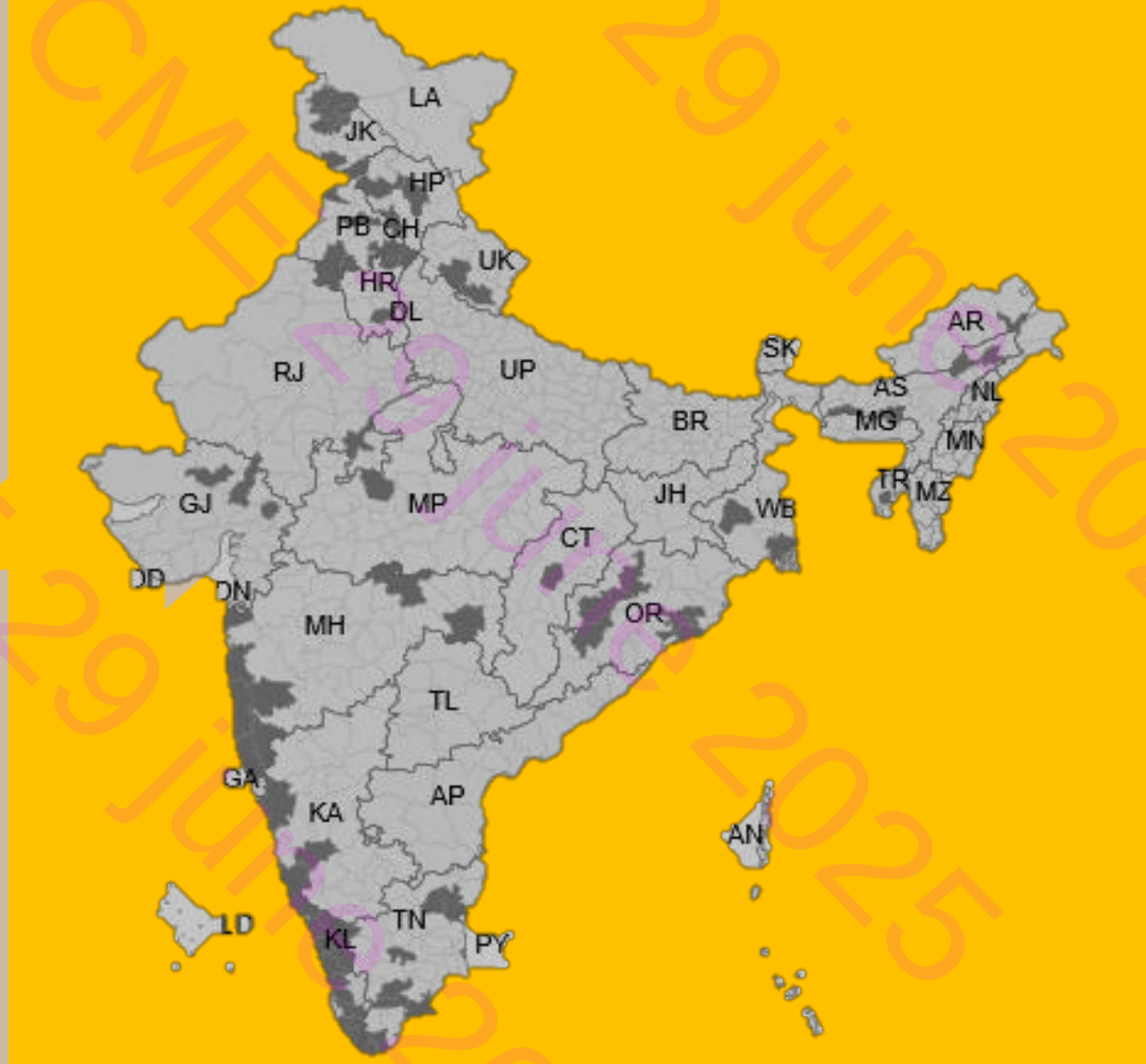
**till 14th May 2023, All news channels are a work of fiction & are for illustration purpose only. 1. . https://idsp.mohfw.gov.in/index4.php?lang=1&level=0&linkid=406&lid=3689 2. http://risingkashmir.com/hepatitis-a-outbreak-among-children-in-bandipora-villages 3. https://www.hindustantimes.com/cities/chandigarh-news/another-child-dies-of-hepatitis-a-in-kashmir-village-4-more-infected-101670786480089.html 4. https://www.cambridge.org/core/journals/epidemiology-and-infection/article/suspected-spread-of-hepatitis-a-virus-from-a-restaurant-rural-area-of-the-kerala-state-india/D8DE5FAC94591362AA87095FF2EC06CA 5. https://medcraveonline.com/JMEN/investigation-of-hepatitis-a-virus-outbreak-in-aligarh-and-its-peripheral-areas-uttar-pradesh-india.html 6. https://timesofindia.indiatimes.com/city/guwahati/groundwater-co-leading-to-hepatitis-outbreak/articleshow/99655332.cms?from=mdr 7. https://www.ndtv.com/india-news/three-more-students-in-rajasthans-kota-test-positive-for-hepatitis-3436960 8. https://timesofindia.indiatimes.com/city/guwahati/four-die-of-hepatitis-a-in-north-guwahati-8-others-in-hospital/articleshow/99627058.cms?from=mdr 9. https://timesofindia.indiatimes.com/city/dehradun/students-test-ve-for-hepatitis-a-doon-hosp-denies-hostel-as-source-of-infection/articleshow/100577819.cms 10. https://timesofindia.indiatimes.com/city/guwahati/medical-camp-held-at-hepatitis-a-outbreak/articleshow/99719142.cms?from=mdr*

Hepatitis A outbreaks in India

***84** districts in India reported outbreaks of Hepatitis A during 2017–2021[1]*

Numerous outbreaks of Hepatitis A in India have been reported to be due to contaminated water of food[2]

Adolescents and young adults aged 1 6–30 years were most affected in India[2]



GoI, Government of India; HAV, hepatitis A virus; MoHFW, Ministry of Health and Family Welfare. *The figure has been adapted from the website of MoHFW, GoI.*[1]

1. Integrated Disease Surveillance Programme. District Wise Viral Hepatitis A Disease Outbreaks India 2017-2021. https://www.idsp.mohfw.gov.in/outbreak_d/Home.html. Accessed July 26, 202

Ways of prevention for Hepatitis A disease

Improved sanitation, food safety and immunization are the most effective ways to combat hepatitis A.[1]

Reduce Feco-oral transmission with adequate supplies of safe drinking water;

Proper disposal of sewage within communities

Personal hygiene practices

Immunization/ Vaccination

1. WHO Hepatitis A. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-a#:~:text=Improved%20sanitation%2C%20food%20safety%20and,of%20sewage%20within%20communities%3B%20and. Accessed July 2023.

What matters while choosing a Hepatitis A vaccine?

Reduced childhood exposure to virus

Increased susceptibility in older children

Increased risk of outbreaks in adults and adulthood

NECESSITATES THE NEED FOR A VACCINE WHICH PROVIDES LONG TERM PROTECTION

1.Arankale et al,Vaccine:Development and Therapy, 2014 . 7–13. 2. Mathur et al, Indian J Med Res. 2008 Dec;128(6):699-704.

Evaluating different Hepatitis A vaccines in India today

GSK

Hepatitis A vaccines

HAVRIX has a duration of persistence expected ***for at least 50 years[1,*]***

Data shown are generated from independent studies – no head-to-head studies have been done comparing HAVRIX with AVAXIM, HEPIBEV/HAVSHIELD or BIOVAC A

Available co-administration data[1,2,5,6]

DTaP, diphtheria, tetanus, acellular pertussis; Hib, Haemophilus influenzae B; IPV, inactivated polio vaccine; PCV, pneumococcal 7-valent conjugate

INACTIVATED VACCINES | *LIVE VACCINE*

HAVRIX[1,2] (GSK)	*AVAXIM[3] (Sanofi)*	*HEPIBEV/ HAVSHIELD[4,5] (BE/ ABBOTT)*	*BIOVAC A (DRL)[6,7]*
Persistence expected for at least 50 yrs[1,*]	***Persistence for ≥10 years***	***Persistence for ≥30 years***	***Persistence for ~17 years***
Modelling – up to at least ***50 years*** *Clinical data –* ***20 years*** 	*Modelling – up to* ***10 years*** *Clinical data –* ***2 years*** 	*Modelling – up to* ***30 years*** *Clinical data –* ***11 years*** 	*Modelling – up to at least* ***17 years*** *Clinical data –* ***17 years*** 
• *Typhoid* • *Yellow fever* • *Cholera (injectable)* • *Tetanus* • *Measles* • *Mumps* • *Rubella* • *Varicella*	• *Typhoid* • *Yellow fever* *(Seroconversion rates were not modified when given with these)*	*No data available*	*No data available*

*1.Agrawal A et al. Infect Dis Ther. 2020;9:785-796. 2. HAVRIX Indian PI Version: PI-HAX/PI/IN/2023/01 dated 19-Jul-2023.3. Avaxim Sanofi PI 4. Hepibev/Havshield PI 5. Wang Y, Qi Y, Xu W, Hu Y, Wang L, Yu Y, Jiang Z, Xia J, Zeng G, Wang Y. Immunogenicity persistence in children of hepatitis A vaccines Healive® and Havrix®: 11 years follow-up and long-term prediction. Hum Vaccin Immunother. 2020 Oct 2;16(10):2559-2564. 6. Biovac PI 7. Wang et al /Vaccines 22 (2004). *A descriptive analysis was used to predict long-term seropositivity results for children based on studies of vaccines containing inactivated hepatitis A antigen either as standalone HAV or combination HAB. In order to extrapolate outcomes in children using data in adults, studies with data on adult vaccine doses of HAB 720 EU or HAV 1,440 EU were selected*

Inactivated vaccines: Deep dive for the immunogenicity data

Immunogenicity study for Chinese origin inactivated vaccine[1,*]

Phase 3, single blind, parallel, randomized, active-controlled, two-arm study in age 1-15 yrs [n=467]

Chinese IHA vaccine[1]	Havrix[1]
~43% Seroprotected subjects^	~39% Seroprotected subjects^
GMC: 183.11 mIU/ML	GMC: 112.29 mIU/ML
40139.65 GMC mIU/ml	18167.84 GMC mIU/ml

(Day 0) **Pre-vaccination status**

(Post Dose 2) **Post-vaccination status**

Immunogenicity study for Havrix[2,*]

Phase IV, open-label, randomized, controlled, multicenter, parallel-group study in age 18–47 months.[n=251]

Havrix[2]
100% Seronegative subjects^
GMC: 1.2 mIU/ML 95% CI ((1.1, 1.3))
>1850 folds rise in GMC

Immunogenicity studies should have a baseline seronegative subjects [1,2]

*Data shown were generated from independent studies, no head to head studies have been performed between the vaccines shown

GMC: Geometric mean concentration; ^>20 mIU/ml Seroprotection level based on WHO definition. 1. Thuluva S et al. Vaccine. 2021;39(49):7166-7174 2. Hemant Jain, Human Vaccines & Immunotherapeutic 10:7, 2089–2097; July 2014

Comparing the available inactivated Hepatitis A Vaccines

GSK

Chinese origin Inactivated Vaccine[1,2,*]		Havrix[3,*]
~43% seroprotected Indian subjects[4]	**Immunogenicity**	100% seronegative Indian subjects[5]
>219 folds rise in seroprotected subjects[4]		>1850 folds rise in seronegative subjects[5]
Not applicable*	**Seroconversion** After a single dose	100% seroconversion in 14-19 days[3,6]
Only one study in China for 11 years [7]		5 studies in low-endemic countries [8]
Studied only in 1 age group (1-8 years)[7]	**Long-term protection**	Studied across age group[8,#]
No annual follow up & limited end points[7]		Annual 20 years follow up[8,#]
Up to 30 years protection[7]		Up to 50 years protection[8,#]

*Data shown were generated from independent studies, no head to head studies have been performed between the vaccines shown

1. Hapibev Prescribing Information 2. Havshiled Prescribing Information 3. Havrix India Prescribing information, version PI-HAX/PI/IN/2023/01 dated 19-Jul-2023; 4. Thuluva S et al. Vaccine. 2021;39(49):7166-7174; July 2014 5. Hemant Jain, Human Vaccines & Immunotherapeutic 10:7, 2089–2097; 6 Abarca K, et al. Int J Infect Dis. 2008 May;12(3):270-7.; 7. Yongji Wang, Yangyang Qi, Wenguo Xu, Hu, Ling Wang, Yongpei Yu, Zhiwei Jiang, Jielai Xia, Gang Zeng & Yalong Wang (2020) Immunogenicity persistence in children of hepatitis A vaccines Healive® and Havrix®: 11 years follow-up and long-term prediction, Human Vaccines & Immunotherapeutics, 16:10, 2559-2564, DOI: 10.1080/21645515.2020.1715687; 8. Agrawal A et al. Infect Dis Ther 2020;9:785–796, #A descriptive analysis was used to predict long-term seropositivity results for children based on studies of vaccines containing inactivated hepatitis A antigen either as standalone HAV or combination HAB. In order to extrapolate outcomes in children using data in adults, studies with data on adult vaccine doses of HAB 720 EU or HAV 1,440 EU were selected

Havrix®
Hepatitis A Vaccine

PRO PROTECTION FROM HEP-A

First
licensed hepatitis A vaccine[1]

29 years
Of real-world experience [1]

150 CTs
Involving >30,000 subjects[1]

>85
countries with HAVRIX^ registered[2]

*Pro: word adapted from professional, expert or someone who has a lot of experience

^HAVRIX Paediatric approved in >85 countries. 1. André F, et al. Expert Rev Vaccines. 2002;1(1)9-23. 2. GSK DOF; 2023N531266_00.

*HAVRIX SAFETY PROFILE**

Havrix Junior has a clinically accepted safety profile in children*

Undesirable effects:

- ***Very common**: Irritability, drowsiness, headaches, pain and redness at injection site*
- ***Common**: Loss of appetite , nausea , swelling, malaise, fever (> 37.5°C)*
- ***Uncommon** : Rhinitis, diarrhea, vomiting , rash , reaction at the injection site (induration)*
- ***Rare**: Hypoaesthesia, paraesthesia , pruritis, shivering Very rare: Neuritis, including Guilliain-Barre syndrome, and transverse myelitis, myalgia, musculoskeletal stiffness*

Contraindications:

- *Hypersensitivity to any component of the vaccine*
- *Those who have shown signs of hypersensitivity during a previous administration of Havrix*

*Havrix Version: PI-HAX/PI/IN/2023/01 dated 19-Jul-2023

*HAVRIX API**

HAVRIX 1440 (ADULT) / 720 (JUNIOR) Inactivated Hepatitis A Vaccine (Adsorbed) IP
ACTIVE INGREDIENT: *HAVRIX1440:* Each dose (1 ml) contains:
Hepatitis A virus antigen (HAV) [HM 175 strain, propagated in MRC5 human diploid cells] 1440 ELISA units; Aluminium (as adjuvant) 0.5 mg [as hydrated Aluminium Oxide IP]. *HAVRIX720 :* Each dose (0.5 ml) contains :
Hepatitis A virus antigen (HAV) [HM 175 strain, propagated in MRC5 human diploid cells] 720 ELISA units ; Aluminium (as adjuvant) 0.25 mg [as hydrated Aluminium Oxide IP] .
INDICATION: For active immunisation against infections caused by hepatitis A virus (HAV) for Children and Adolescents (from 1 year up to and including 18 years of age) and adults (from age 19 years and onwards). The booster dose may be given at any time between 6 months and 5 years, but preferably between 6 and 12 months after the primary dose. **DOSAGE AND ADMINISTRATION:** ***Posology Primary Vaccination-*** Adults from age 19 years and onwards a single dose of *HAVRIX* 1440 Adult (1.0 ml suspension) is used for primary immunisation. 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 immunisation. ***Booster vaccination-*** After primary vaccination with either *HAVRIX* 1440 Adult or *HAVRIX* 720 Junior, a booster dose is recommended in order to ensure long term protection. This booster dose should be given at any time between 6 months and 5 years, but preferably between 6 and 12 months after the primary dose. ***Method of Administration-****HAVRIX* must be injected intramuscularly only. It is recommended to inject the vaccine in the deltoid region in adults and in children. The deltoid muscle is not yet sufficiently developed in very young children, so the vaccine should be administered in the anterolateral part of the thigh. The injection must not be administered in the gluteal region subcutaneously or intradermally because the antibody response might be suboptimal. However, the vaccine should be administered subcutaneously in patients suffering from thrombocytopoenia or subject to serious haemorrhage (e.g. haemophiliacs) because bleeding could occur after intramuscular administration in such persons. Strong pressure should be exercised at the site of the injection (without rubbing) for at least 2 minutes. The vaccine may never be administered intravascularly.
CONTRA-INDICATIONS: *HAVRIX* may not be administered to persons with a known hypersensitivity to a component of the vaccine or to those who have shown signs of hypersensitivity during a previous administration of *HAVRIX*.
SPECIAL WARNINGS and SPECIAL PRECAUTIONS:
As in the case of other vaccines, *HAVRIX* will not be administered to patients with an acute febrile illness. A common infection does not constitute a contra-indication, however. People may already be in the incubation period of hepatitis A at the time of vaccination. In such circumstances, it is not certain that *HAVRIX* will prevent hepatitis A. In patients undergoing haemodialysis and in subjects with a deficient immune system, the anti-HAV (hepatitis A virus) may remain insufficient after a primo-vaccination; in such patients, additional doses of the vaccine may have to be administered to attain an adequate antibody count. *HAVRIX* may contain traces of neomycin. The vaccine will have to be used with caution in patients with a known hypersensitivity to this antibiotic. As with every product administered parenterally, it is recommended to prepare an appropriate medical treatment for immediate use, if an anaphylactic reaction were to occur after the administration of the vaccine. For this reason, the vaccinated persons should remain under medical supervision for half an hour after vaccination.
Syncope (fainting) can occur after any vaccination, or even before with adolescents in particular, as a psychogenic reaction to injection. This can be accompanied by several neurological signs such as a transient disturbance in vision, paraesthesia and tonic-clonic movements of the limbs during the recovery phase. It is important that caution be set up to avoid injuries in the event of fainting. *HAVRIX* may be administered with persons who are HIV positive. Vaccination is not justified in subjects with anti-hepatitis A IgG. This vaccine contains less than 1 mmol of sodium (23 mg) and potassium less than 1 mmol (39 mg) per dose, it is therefore essentially ‘sodium-free’ and ‘potassium-free’.

ADVERSE EFFECTS:
Clinical Trials: Frequencies, per dose, are defined as follows: Very common: ≥ 1/10, Common: ≥ 1/100 to < 1/10, Uncommon: ≥1/1000 to < 1/100, Rare: ≥1/10000 to < 1/1000, Very rare: < 1/10000.
Undesirable effects reported with HAVRIX Junior 720
Infections and infestations : Uncommon: rhinitis, Metabolism and nutrition disorders Common: loss of appetite, Psychiatric disorders Very common: irritability Nervous system disorders Common: drowsiness, headaches; Very rare: neuritis, including Guillain-Barré syndrome and transverse myelitis, Gastrointestinal disorders Common: nausea Uncommon: diarrhoea, vomiting, Skin and subcutaneous tissue disorders Uncommon: rash, General disorders and administrative site conditions Very common: pain and redness at injection site Common: swelling, malaise, fever (> 37.5°C) Uncommon: reaction at the injection site (induration)
Undesirable effects reported with HAVRIX 1440
Infections and infestations Uncommon: upper respiratory tract infection, rhinitis , Metabolism and nutrition disorders Common: loss of appetite, Nervous system disorders Very common: headaches Uncommon: dizziness Rare: hypoaesthesia, paraesthesia Very rare: neuritis, including Guiliain-Barré syndrome and transverse myelitis, Gastrointestinal disorders: Common: gastrointestinal syndromes, diarrhoea, nausea Uncommon: vomiting, Skin and subcutaneous tissue disorders Rare: pruritis, Musculoskeletal and systemic disorders: Uncommon: myalgia, musculoskeletal stiffness, General disorders and administrative site conditions Very common: pain and redness at injection site, fatigue Common: swelling, malaise, fever (>37.5°C), reaction at the injection site (induration)Uncommon: influenza like illness Rare: shivering
Post-marketing surveillance
Immune system disorders Anaphylactic reactions, allergic reactions, including anaphylactoid reactions and serum sickness like disease, Nervous system disorders Convulsions, Vascular disorders Vasculitis, Skin and subcutaneous tissue disorders Angioneurotic oedema, urticaria, erythema multiforme, Musculoskeletal and connective tissue disorders Arthralgia
Version: HAX/API/IN/2021/01 v01 dated 08 Jan 2021
Refer to full prescribing information before prescribing.
Full Prescribing information available on request from GlaxoSmithKline Pharmaceuticals Limited, Dr. Annie Besant Road, Worli, Mumbai 400 030 (India).
Registered medical practitioners can refer company website http://india-pharma.gsk.com/enin/products/prescribing-information/ for full Product Information.
Please report adverse events with any GSK product to the company at india.pharmacovigilance@gsk.com

**Havrix Version: HAX/API/IN/2021/01 v01 dated 08 Jan 2021*

While fighting Hep A, you don't just protection. You need pro*-protection with Havrix

THANK YOU!

*Pro: word adapted from professional, expert or someone who has a lot of experience

PM-IN-HAV-PPT-240004, DoP March 2023