

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hepatyrix, suspension for injection.
Hepatitis A (inactivated) and Typhoid Polysaccharide vaccine (adsorbed).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (1 ml) contains:

Hepatitis A virus (HM175 strain) (inactivated) ¹	1440 ELISA Units
Vi polysaccharide of <i>Salmonella typhi</i> (Ty2 strain)	25 micrograms

¹ Produced in human diploid (MRC-5) cells	
Adsorbed on aluminium hydroxide, hydrated	0.5 milligrams Al ³⁺

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection.
Hepatyrix is a slightly opaque white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hepatyrix is indicated for active immunisation against hepatitis A virus infection and typhoid fever in adults and adolescents 15 years of age and older.

Hepatyrix should be given in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Primary vaccination

A single dose of 1.0 ml is recommended for both adults and adolescents aged 15 years and older.
The vaccine should be given at least two weeks prior to risk of exposure to typhoid and hepatitis A (see section 5.1 for immunogenicity data).

Booster vaccination

In order to provide long term protection against infection caused by hepatitis A virus, a booster dose of an inactivated hepatitis A vaccine is recommended at any time between 6 and 12 months after a single dose of Hepatyrix.

Hepatyrix may also be given as a single dose of 1.0 ml for booster vaccination between 6 and 12 months following primary immunisation with an inactivated hepatitis A vaccine to subjects who also require protection against typhoid fever.

Subjects who remain at risk of typhoid fever should be revaccinated using a single dose of Vi polysaccharide vaccine every 3 years (see section 5.1). Hepatyrix may be used to revaccinate against typhoid fever in subjects that also need to

have a dose of hepatitis A vaccine.

Paediatric population

The safety and efficacy of Hepatyrix in subjects under 15 years of age have not been established.

Method of administration

Hepatyrix is for intramuscular administration in the deltoid region.

The vaccine should not be administered in the gluteal region.

Hepatyrix should under no circumstances be administered intravascularly.

Hepatyrix should not be administered subcutaneously/intradermally since administration by these routes may result in a suboptimal response to the vaccine.

In exceptional circumstances, Hepatyrix may be administered subcutaneously to subjects with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular administration to these subjects. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes after the injection.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or to neomycin.

Hypersensitivity to a previous administration of Hepatyrix or a dose of either of the monovalent vaccines Havrix and Typherix.

As with other vaccines, the administration of Hepatyrix should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contra-indication for vaccination.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

In subjects with an impaired immune system, adequate anti-HAV and anti-Vi antibody titres may not be obtained after a single dose of Hepatyrix and such patients may therefore require administration of additional doses of vaccine. If possible, vaccination should be delayed until the completion of any immunosuppressive treatment. Subjects with chronic immunodeficiency such as HIV infection may be vaccinated if the underlying immunodeficiency allows the induction of an antibody response, even if limited.

It is possible that subjects may be in the incubation period of a hepatitis A infection at the time of vaccination. It is not known whether Hepatyrix will prevent clinically apparent hepatitis A infections in such cases.

Hepatyrix will not prevent infection caused by other hepatitis-causing agents such as hepatitis B virus, hepatitis C virus, hepatitis E virus or other pathogens known to infect the liver.

Hepatyrix protects only against typhoid fever caused by *Salmonella enterica serotype Typhi*. Protection is not conferred against paratyphoid fever or infections with any other serotypes of *S. enterica*.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

4.5 Interaction with other medicinal products and other forms of interaction

Hepatyrix must not be mixed with any other vaccine in the same syringe.

If Hepatyrix is to be given at the same time as (an)other injectable vaccine(s), the vaccines should always be administered at different injection sites.

Hepatyrix contains purified inactivated hepatitis A antigen and purified Vi capsular polysaccharide. Although concomitant use with other inactivated vaccines has not specifically been studied, it is anticipated that no interaction will be observed.

Concomitant administration of yellow fever vaccine with Hepatyrix has not been specifically assessed. However, based on data obtained from the concomitant administration of various monovalent vaccines (purified Vi polysaccharide typhoid vaccine or inactivated hepatitis A vaccine) with yellow fever vaccine, no interference with the immune responses to any of these antigens would be expected.

The effect of concomitant administration of immunoglobulins on the immunogenicity of Hepatyrix has not been assessed. Therefore, interference with the immune response cannot be ruled out.

4.6 Fertility, pregnancy and lactation

Pregnancy

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available. Hepatyrix should only be used after careful consideration of the risk-benefit relationship.

Breast-feeding

Adequate data on the administration of Hepatyrix to women who are breast-feeding their infants are not available. Hepatyrix should be used during breast-feeding only when clearly needed.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under *section 4.8 —Undesirable effects* may affect the ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

In controlled clinical studies, the most commonly reported reactions after administration of Hepatyrix were those at the site of injection. All local and general symptoms resolved without any sequelae.

Tabulated summary of adverse reactions

Frequencies are reported as:

Very common: ($\geq 1/10$)

Common: ($\geq 1/100$ to $< 1/10$)

Uncommon: ($\geq 1/1,000$ to $< 1/100$)

Rare: ($\geq 1/10,000$ to $< 1/1,000$)

Very rare: ($< 1/10,000$)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse reactions
Clinical trials		
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Nausea
Skin and subcutaneous tissue disorders	Very common	Erythema
	Common	Itching
General disorders and administration site conditions	Very common	Pain
	Common	Fever, general aches, malaise, swelling
Post-marketing surveillance		
Immune system disorders	Very rare	Allergic reactions, including anaphylaxis and anaphylactoid reactions
Nervous system disorders	Very rare	Syncope
Skin and subcutaneous tissue disorders	Very rare	Skin rashes

Experience with the GlaxoSmithKline monovalent hepatitis A vaccine:

System Organ Class	Frequency	Adverse reactions
Clinical trials		
Metabolism and nutrition disorders	Common	Loss of appetite
Gastrointestinal disorders	Common	Vomiting
Post-marketing surveillance		
Nervous system disorders	Very rare	Neurological manifestations including transverse myelitis, Guillain-Barre syndrome and neuralgic amyotrophy, convulsions
Musculoskeletal and connective tissue disorders	Very rare	Arthralgia, myalgia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.
Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacterial and viral vaccines combined, ATC code J07CA10

Hepatyrix confers immunity against typhoid fever and HAV infection by inducing specific anti-Vi and anti-HAV antibodies.

In clinical studies involving 462 subjects of 15-50 years of age, seropositivity rates for anti-HAV and anti-Vi antibodies

were 89.8% and 97.5% respectively two weeks after primary immunisation. At month 1, seropositivity rates for anti-HAV and anti-Vi antibodies were 99.0% and 95.7% respectively.

In a clinical study where a group of 99 subjects received a booster dose of hepatitis A vaccine 12 months following the initial dose of Hepatyrix, all subjects were seropositive for anti-HAV antibodies one month later (i.e. at month 13).

When Hepatyrix was given 12 months following primary vaccination with the hepatitis A vaccine in a cohort of 97 subjects, the seropositivity rates for anti-Vi and anti-HAV antibodies were 88.2% and 100% respectively one month later (i.e. at month 13).

In two long-term clinical studies (TypHA-002 and TypHA-009), the persistence of anti-Vi and anti-HAV antibodies has been evaluated up to 36 months after vaccination with Hepatyrix and a booster dose of Havrix 1440 (GlaxoSmithKline Biologicals monovalent inactivated hepatitis A vaccine) administered six months later. In one of these two studies TypHA-009) the seropositivity rates obtained with Hepatyrix were compared to those obtained with co-administration of Typherix (GlaxoSmithKline Biologicals monovalent purified Vi polysaccharide vaccine) and Havrix 1440, followed by a booster dose of Havrix 1440 administered six months later.

The anti-Vi seropositivity rates observed in these two studies are presented below:

	TypHA-002		TypHA-009			
	Hepatyrix		Hepatyrix		Typherix +Havrix 1440	
	N	Anti-Vi seropositivity rate (%)	N	Anti-Vi seropositivity rate (%)	N	Anti-Vi seropositivity rate (%)
Day 14	128	97.7	217	96.3	230	97.4
Month 1	138	97.8	223	96.4	232	97.4
Month 12	120	73.3	211	80.6	210	85.7
Month 24	97	46.4	209	68.4	207	72.0
Month 36	113	53.1	195	55.9	192	65.1

N: number of vaccinees
Anti-Vi seropositivity rate (%): percentage of vaccinees with antibody titres ≥ assay cut-off (≥ 150 EL.U/ml)

In another clinical study (TypHA-010/011), subjects who had received a dose of Hepatyrix six years previously were given a dose of Typherix. Before Typherix was administered 15 of 39 subjects (38%) were seropositive for anti-Vi antibody. At one month after vaccination with Typherix the seropositivity rate was 92%. At one year after the dose of Typherix the anti-Vi seropositivity rate was 84%. The anti-Vi seropositivity rates and the geometric means concentrations of anti-Vi antibody at Months 1 and 12 after the dose of Typherix were comparable with the corresponding values observed previously in these subjects after a dose of Hepatyrix.

In studies TypHA-002 and TypHA-009, one month after the booster dose of Havrix 1440 (i.e. at month 7) the anti-HAV seropositivity rate observed was 100%. At month 36 at least 99% of the vaccinees were still seropositive with respect to anti-HAV antibodies.

Based on data generated after administration of a booster dose of a monovalent hepatitis A vaccine between six and twelve months following the initial dose of the monovalent hepatitis A vaccine, it is predicted that anti-HAV antibodies persist for many years (at least 10 years).

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Store in the original package in order to protect from light.

Do not freeze. Discard if vaccine has been frozen.

6.5 Nature and contents of container

1 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber). Pack sizes of 1 and 10 with needles. Packs of 1, 10, 20 and 50 without needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The vaccine's normal appearance is a cloudy white suspension, which may sediment during storage. Shake the container well to distribute the suspension uniformly before administering the vaccine.

The vaccine should be inspected visually for extraneous particulate matter and/or discolouration prior to administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1077/099/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 22 June 2009

10 DATE OF REVISION OF THE TEXT

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