TWINRIX

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

TWINRIX

Inactivated hepatitis A virus (HAV) and recombinant-DNA hepatitis B virus (HBV) surface antigen vaccine.

Suspension for injection.

COMPOSITION:

Each 1,0 mL contains:

Hepatitis A virus antigen	720 ELISA units
r-DNA hepatitis B virus surface antigen	20 µg

Sugar-free.

Excipients: Aluminium hydroxide, aluminium phosphate, sodium chloride, water for injections.

Residues: Amino acids for injection, formaldehyde, neomycin sulphate, polysorbate 20, residual tris and phosphate buffer.

PHARMACOLOGICAL CLASSIFICATION:

A 30.2 Antigens

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

TWINRIX induces in the recipient a specific immunity against HAV and HBV infection by inducing specific anti-HAV and anti-HBs antibodies.

In clinical studies involving subjects aged 1 to 15 years old, seropositivity rates for anti-HAV antibodies were 99,1 % one month after the first dose and 100 % after the second dose given at month 6 (i.e., month 7). Seropositivity rates for anti-HBs antibodies were 74,2 % one month after the first dose and 100 % after the second dose given at month 6 (i.e., month 7). The anti-HBs seroprotection rates (titers = 10 mIU/mL) at these time points were 37,4 % and 98,2 % respectively.

When the second dose was administered at month 12, seropositivity rates for anti-HAV were 99,0 % and seropositivity rates for anti-HBs were 99,0 % at month 13 with seroprotection rates of 97,0 %.

In a comparative study conducted in adolescents (using the 2 dose schedule) vs. an alternative schedule comprising of 3 doses of the combined vaccine containing 360 ELISA units inactivated HA virus and 10 µg HBsAg in a dose volume of 0,5 mL, seroprotection rates for anti-HBs at intermediate time points before the second dose of TWINRIX were lower compared to those obtained with the alternative schedule comprising 3 doses, but that non-inferiority was shown after completion of the schedule (month 7).

Anti-HAV and anti-HBs antibodies have been shown to persist for at least 24 months following the initiation of a 0-, 6-month schedule of TWINRIX. Seropositivity rates were 100 % and 94,2 % respectively for anti-HAV and anti-HBs antibodies at month 24. The seroprotection rate for anti-HBs at this time point was 93,3 %. In this study, the immune response for both antigen components was comparable to that seen after a 3-dose regimen of the combined vaccine containing 360 ELISA units of inactivated hepatitis A virus and 10 µg of recombinant hepatitis B surface antigen in a dose volume of 0,5 mL.

The persistence of anti-HAV and anti-HBs antibodies at month 24 was shown to be similar following a 0-, 6-month or a 0-, 12-month schedule.

In adults aged 16 years and above, administered with a three-dose schedule of TWINRIX, protection against hepatitis A and hepatitis B develops within 2-4 weeks. In the clinical studies, specific humoral antibodies against hepatitis A were observed in approximately 94 % of the adults one month after the first dose and in 100 % one month after the third dose (i.e., month 7). Specific humoral antibodies against hepatitis B were observed in 70 % of the adults after the first dose and approximately 99 % after the third dose.

For use in exceptional circumstances in adults, the 0-, 7- and 21-day primary schedule, plus a fourth dose at month 12 results in 82 % and 85 % of vaccinees having seroprotective levels of anti-HBV antibodies at 1 and 5 weeks respectively following the third dose. One month after the fourth dose, all vaccinees demonstrated seroprotective levels of antibody. Seropositivity rates for anti-HAV antibodies were 100 % and 99,5 % at 1 and 5 weeks respectively following the third dose and reached 100 % one month after the fourth dose.

In a clinical study conducted in subjects over 40 years of age, the seropositivity rate for anti-HAV antibodies and seroprotection rate against hepatitis B following TWINRIX on a 0-, 1- and 6-month schedule were compared with the seropositivity and seroprotection rates of monovalent hepatitis A and B vaccines when administered separately.

The seroprotection rates against hepatitis B after the administration of TWINRIX were 92 % and 57 % at 7 and 48 months following the first dose respectively, versus 80 % and 40 % after the GlaxoSmithKline Biologicals monovalent 20 µg hepatitis B vaccine, and 71 % and 27 % after another licensed monovalent 10 µg hepatitis B vaccine. In all groups, anti-HBs antibody concentrations decreased as age and body mass index increased; concentrations were also lower in males compared with females.

The seropositivity rates for anti-HAV antibodies after TWINRIX were 97 % at both 7 and 48 months following the first dose versus 99 % and 94 % after the GlaxoSmithKline Biologicals monovalent hepatitis A vaccine and 99 % and 96 % after another licensed monovalent hepatitis A vaccine.

Subjects received an additional dose of TWINRIX to assess the immune memory 48 months after the first dose of the primary vaccination course with the same vaccine. One month after this dose, 95 % of subjects elicited anti-HBV antibody concentration ≥ 10 mIU/mL and Geometric Mean Concentrations (GMC) increased by 179-fold (GMC of 7233,7 mIU/mL) indicative of an immune memory response.

In two long term clinical studies conducted in adults, 15 years after the primary vaccination with TWINRIX, the anti-HAV seropositivity rates were 100 % in both studies and the anti-HBs seroprotection rates were 89,3 % and 92,9 % respectively.

The kinetics of decline of anti-HAV and anti-HBs antibodies were shown to be similar to those of the monovalent vaccines.

Pharmacokinetic properties:

Evaluation of pharmacokinetics is not required for vaccines.

INDICATIONS:

TWINRIX is indicated for active immunisation against hepatitis A and hepatitis B virus infection in adults and children aged from 1 year upwards.

It can be expected that hepatitis D will also be prevented by immunisation with TWINRIX as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

CONTRAINDICATIONS:

The administration of TWINRIX should be postponed in subjects suffering from acute, severe febrile illness. The presence of a minor infection, however, is not a contraindication for vaccination.

TWINRIX should not be administered to subjects with known hypersensitivity to any constituent of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of TWINRIX or the monovalent hepatitis A or hepatitis B vaccine.

WARNINGS AND SPECIAL PRECAUTIONS:

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.

It is possible that subjects may be in the incubation period of a hepatitis A or hepatitis B infection at the time of vaccination. It is not known whether TWINRIX will prevent hepatitis A and hepatitis B in such cases.

The vaccine will not prevent infection caused by other agents such as hepatitis C and hepatitis E and other pathogens known to infect the liver.

In haemodialysis patients and persons with an impaired immune system, adequate anti-HAV and anti-HBs antibody titres may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine.

TWINRIX SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY.

TWINRIX should not be mixed with other vaccines in the same syringe.

TWINRIX is not recommended for post-exposure prophylaxis (e.g., needle stick injury).

Appropriate medical treatment, including adrenaline, should always be readily available in cases of a rare anaphylactic event following the administration of the vaccine.

INTERACTIONS:

Clinical studies have demonstrated that TWINRIX can be administered concomitantly with, either diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus*

influenzae type b (DTPa-IPV/Hib) or Measles-Mumps-Rubella vaccines in the second year of life. In these trials, the injectable vaccines were given at different injection sites.

Although the concomitant administration of TWINRIX and other vaccines has not specifically been studied, it is anticipated that, if different syringes and other injection sites are used, no interaction will be observed.

In patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immunologic response may not be achieved.

PREGNANCY AND LACTATION:

TWINRIX should be used during pregnancy only when clearly needed, and when the possible advantages outweigh the possible risks for the foetus.

Adequate human data on use during lactation and adequate animal reproduction studies are not available. Therefore, TWINRIX should be used with caution in breastfeeding women.

DOSAGE AND DIRECTIONS FOR USE:

TWINRIX should be injected intramuscularly in the deltoid region of the upper arm in adults and older children. The anterolateral thigh may be used in infants.

However, it should be administered subcutaneously to subjects with thrombocytopenia or bleeding disorders, since bleeding may occur following intramuscular administration to these subjects.

The recommended dose for adults and children aged from 1 year upwards is 1,0 mL.

Primary vaccination schedule:

Adults and adolescents of 16 years of age and above:

The standard primary course of vaccination with TWINRIX consists of three doses, the first administered at the elected date, the second one month later and the third six months after the first dose.

In exceptional circumstances in adults, when travel is anticipated within one month or more after initiating the vaccination course, but where insufficient time is available to allow the standard 0-, 1-, 6-month schedule to be completed, a schedule of three intramuscular injections given at 0-, 7- and 21-days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose.

Children of 1 to 15 years of age:

The standard primary course of vaccination with TWINRIX consists of two doses, the first is administered at the elected date and the second between six and twelve months after the first dose. As protection against hepatitis B infection will not be obtained in all vaccinees until after the second dose, it is important that the second dose be administered to assure protection against hepatitis B infection.

Booster dose:

Long-term antibody persistence data following vaccination with TWINRIX in adults with a 0-, 1-, 6-month schedule are available for up to 60 months after vaccination.

The anti-HBs and anti-HAV antibody titres observed following a primary vaccination course with the combined vaccine are in the range of what is seen following vaccination with the monovalent vaccines. The kinetics of antibody decline are also similar. General guidelines for booster vaccination can therefore be drawn from experience with the monovalent vaccines.

- **Hepatitis B**

The need for a booster dose of hepatitis B vaccine in healthy individuals who have received a full primary vaccination course has not been established; however, some official vaccination programmes currently include a recommendation for a booster dose of hepatitis B vaccine and these should be respected.

For some categories of subjects or patients exposed to HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure a protective antibody level ≥ 10 IU/l.

- **Hepatitis A**

  It is not yet fully established whether immunocompetent individuals who have responded to hepatitis A vaccination will require booster doses, as protection in the absence of detectable antibodies may be ensured by immunological memory. Guidelines for boosting are based on the assumption that antibodies are required for protection; anti-HAV antibodies have been predicted to persist for at least 10 years.

  In situations where a booster dose of both hepatitis A and hepatitis B are desired, TWINRIX can be given. Alternatively, subjects primed with TWINRIX may be administered a booster dose of either of the monovalent vaccines.

Use and Handling:

TWINRIX should be resuspended before use. When resuspended, the vaccine will have a uniform hazy white appearance.

Upon storage, a fine white deposit with a clear colourless layer above may be observed.

Resuspension of the vaccine to obtain a uniform hazy white suspension.

The vaccine can be resuspended following the steps below.

1. Hold the syringe upright in a closed hand.
2. Shake the syringe by tipping it upside down and back again.

3. Repeat this action vigorously for at least 15 seconds.
4. Inspect the vaccine again:
   - If the vaccine appears as a uniform hazy white suspension, it is ready to use – the appearance should not be clear.
   - If the vaccine still does not appear as a uniform hazy white suspension - tip upside down and back again for at least another 15 seconds - then inspect again.

The vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the vaccine.

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

SIDE EFFECTS:

Clinical trials:

The safety profile presented below is based on data from more than 6 000 subjects who received either, the standard 0-, 1-, 6-month schedule or the accelerated 0-, 7-, 21- days schedule.

In a comparative study, it was noted that the frequency of solicited adverse events following the administration of TWINRIX is not different from the frequency of solicited adverse events following the administration of the monovalent vaccines.

Frequencies are reported as:

Very common: (≥ 1/10)

Common: (≥ 1/100, < 1/10)

Uncommon: (≥ 1/1 000, < 1/100)

Rare: (≥ 1/10 000, < 1/1 000)

Very rare: (≤ 1/10 000) including isolated reports.

Infections and infestations:

Uncommon: upper respiratory tract infection

Blood and lymphatic system disorders:

Rare: lymphadenopathy

Metabolism and nutrition disorders:

Rare: decreased appetite

Psychiatric disorders:

Common: irritability

Nervous system disorders:

Very common: drowsiness, headache

Uncommon: dizziness

Rare: hypoaesthesia, paraesthesia

Vascular disorders:

Rare: hypotension

Gastrointestinal disorders:

Common: gastrointestinal symptoms (such as diarrhoea, nausea, vomiting)

Skin and subcutaneous tissue disorders:

Rare: rash, pruritus

Very rare: urticaria

Musculoskeletal and connective tissue disorders:

Uncommon: myalgia

Rare: arthralgia

General disorders and administration site conditions:

Very common: pain and redness at the injection site, fatigue

Common: swelling at the injection site, injection site reaction, malaise

Uncommon: fever (≥ 37,5 °C)

Rare: influenza like illness, chills.

In a clinical trial where TWINRIX was administered at 0-, 7-, 21-days, solicited general symptoms were reported with the same categories of frequency as defined above. After a fourth dose given at month 12, the incidence of systemic adverse reactions was comparable to that seen after vaccination at 0-, 7-, 21-days.

Post marketing surveillance:

Infections and infestations: meningitis

Blood and lymphatic system disorders: thrombocytopenia, thrombocytopenic purpura

Immune system disorders: anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness

Nervous system disorders: encephalitis, encephalopathy, neuritis, neuropathy, paralysis, convulsions

Vascular disorders: vasculitis

Skin and subcutaneous tissue disorders: angioneurotic oedema, lichen planus, erythema multiforme

Musculoskeletal and connective tissue disorders: arthritis, muscular weakness

Very common: drowsiness, headache

General disorders and administration site conditions*:* immediate injection site pain, stinging and burning sensation.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

IDENTIFICATION:

A clear glass syringe containing a turbid liquid after shaking with a slow settling white deposit. The supernatant is colourless. The precipitate is easily brought into suspension when shaken.

PRESENTATION:

TWINRIX is presented as a single dose of 1,0 mL suspension in a pre-filled glass syringe (type I glass) with a plunger stopper (bromobutyl rubber) and with a rubber tip cap.

The tip cap and rubber plunger stopper of the pre-filled syringe are not made with natural rubber latex.

STORAGE INSTRUCTIONS:

Store between +2 °C and +8 °C.

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

DO NOT FREEZE - discard if the vaccine has been frozen.

Keep out of reach of children.

REGISTRATION NUMBER:

32/30.1/0244

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

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