1. NAME OF THE MEDICINAL PRODUCT

AVAXIM 160 U, suspension for injection in a pre-filled syringe.
Hepatitis A vaccine (inactivated, adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 0.5 millilitre dose contains:
Hepatitis A virus, GBM strain (inactivated)[1, 2]……160 EU[3]
[1] produced in human diploid (MRC-5) cells
[2] adsorbed on aluminium hydroxide, hydrated (0.3 milligrams Al^{3+})
[3] ELISA Unit. In the absence of an international standardised reference, the antigen content is expressed using an in- house reference
Excipient(s) with known effect:
Ethanol anhydrous…….2.5 microlitres
Phenylalanine……10 micrograms
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a pre-filled syringe.
Hepatitis A vaccine (inactivated, adsorbed) is a cloudy and white suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

This vaccine is indicated for active immunisation against infection caused by the hepatitis A virus in adolescents over the age of 15 and in adults.

The vaccine does not protect against infection caused by hepatitis B, hepatitis C, or hepatitis E viruses, or any other known liver pathogens.

Transmission of the hepatitis A virus is usually through the ingestion of contaminated water or food. Persons in contact with contaminated subjects are usually infected through the oro-faecal route.

The possibility of transmission by blood or by sexual con (oral-anal relations) has also been demonstrated.

This vaccine should be administered in accordance with official recommendations.

4.2. Posology and method of administration

Posology
The recommended dosage for subjects over the age of 15 is 0.5 ml.
The initial protection is obtained after one single injection.

In order to obtain a long-term protection against infections caused by the Hepatitis A virus, in adolescents over the age of 15 and in adults, a booster dose should be administered, preferably between 6 and 12 months after the first vaccination and can be administered up to 36 months after the first vaccination (see section 5.1). It is estimated that HAV antibodies persist several years (at least 10 years) after the second dose (booster).

This vaccine can also be administered as a booster dose of the Hepatitis A vaccination in subjects over the age of 15 who have received the first injection with the combined Typhoid Fever (Vi purified polysaccharide) and Hepatitis A (inactivated) vaccine between 6 and 36 months earlier.

Method of administration
Because the vaccine is adsorbed, it is recommended to administer this vaccine by the intramuscular route (IM) to minimise local reactions.
The recommended injection site is the deltoid muscle.
In exceptional cases, the vaccine may be administered by the subcutaneous route in patients suffering from thrombocytopenia or in patients at risk of haemorrhage.
The vaccine is not to be injected into the buttocks because of the variability of this anatomical site (presence of varying amounts of adipose tissue), nor administered intradermally, since these methods of administration may induce a weaker immune response.
Do not inject by the intravascular route: ensure that the needle does not penetrate a blood vessel. This vaccine must not be mixed with other vaccines in the same syringe.

4.3. Contraindications

• Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 or to neomycin, which may be present in the vaccine in trace amounts.
• Hypersensitivity following a previous injection of this vaccine.
• Vaccination should be delayed in subjects with an acute severe febrile illness.

4.4. Special warnings and precautions for use

As with all vaccines, appropriate medical treatment and supervision should be readily available for immediate use in case of rare anaphylactic reaction following vaccination. AVAXIM 160 U should only be given by a physician or health care worker trained in the administration of vaccines.

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.
AVAXIM 160 U has not been studied in patients with impaired immunity. The immune response to AVAXIM 160 U could be impaired by immunosuppressive treatment or in immunodeficiency states. In such cases, it is recommended to measure the antibody response to be sure of protection and, if possible, to wait for the end of any suppressive treatment before vaccination. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended although the antibody response may be limited.
Because of the incubation period of hepatitis A, infection may be present but not clinically apparent at the time of vaccination. The effect of AVAXIM 160 U on individuals late in the incubation period of hepatitis A has not been documented.
Individuals having grown up in areas of high endemicity and/or with a history of jaundice may be immune to hepatitis A, in which case the vaccine is unnecessary. Testing for antibodies to hepatitis A prior to a decision on immunisation should be considered in such situations. If not, seropositivity against hepatitis A is not a contraindication. AVAXIM 160 U is as well tolerated in seropositive as in seronegative subjects (see Section 4.8).
AVAXIM 160 U does not provide protection against infection caused by hepatitis B virus, hepatitis C virus, hepatitis E virus or by other liver pathogens.
As no studies have been performed with AVAXIM 160 U in subjects with liver disease, the use of this vaccine in such subjects should be considered with care.
As with any vaccine, vaccination may not result in a protective response in all susceptible vaccinees.

<u>AVAXIM 160 U contains ethanol, phenylalanine, potassium and sodium</u>
AVAXIM 160 U contains small amounts of ethanol (alcohol), less than 100 mg per dose.
AVAXIM 160 U contains 10 microgram phenylalanine in each 0.5 ml dose which is equivalent to 0.17 microgram/kg for a 60 kg person. Phenylalanine may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
AVAXIM 160 U contains less than 1mmol of potassium (39 mg) and sodium (23 mg) per dose, that is to say essentially 'potassium-free' and 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

No clinical data on concomitant administration of AVAXIM 160 U with other inactivated vaccine(s) or recombinant hepatitis B virus vaccine have been generated. When concurrent administration is considered necessary, AVAXIM 160 U must not be mixed with other vaccines in the same syringe, and other vaccines should be administered at different sites with different syringes and needles.

Seroconversion rates were not modified when AVAXIM 160 U was given at the same time as but at a different injection site to a Vi polysaccharide typhoid vaccine or a yellow fever vaccine reconstituted with a Vi polysaccharide typhoid vaccine.

Concomitant administration of immunoglobulin and AVAXIM 160 U at two separate sites may be performed. Seroconversion rates are not modified, but antibody titres could be lower than after vaccination with AVAXIM 160 U alone. Therefore, consideration should be given to whether or not the subject is likely to be at long-term risk of exposure.
No interaction with other medicinal products is currently known.

4.6. Pregnancy and lactation

Pregnancy
There are no adequate data from the use of hepatitis A vaccine (inactivated, adsorbed) in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development. The potential risk for humans is unknown.
AVAXIM 160 U should not be used during pregnancy unless clearly necessary and following an assessment of the risks and benefits

Breastfeeding
The use of this vaccine is possible during breast-feeding.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Adverse event data are derived from clinical trials and worldwide post-marketing experience.
Within each system organ class, the adverse events are ranked under headings of frequency, most frequent reactions first, using the following convention:
Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10000, <1/1000), Very rare (<1/10000).

Clinical Studies
In clinical trials, adverse reactions were usually mild and confined to the first few days after vaccination with spontaneous recovery. The adverse reactions observed with AVAXIM 160 U were:
Nervous system disorders
Common: headache
Gastrointestinal disorders
Common: nausea, vomiting, decreased appetite, diarrhoea, abdominal pain
Musculoskeletal and connective tissue disorders
Common: myalgia/arthralgia
General disorders and administration site conditions

Very common: asthenia, mild injection site pain
Common: mild fever
Uncommon: injection site erythema
Rare: injection site nodule
Investigations
Rare: transaminases increased (mild and reversible)

Reactions were less frequently reported after the booster dose than after the first dose.

In subjects seropositive against hepatitis A virus, AVAXIM 160 U was as well tolerated as in seronegative subjects.

Post marketing experience
Based on spontaneous reporting, the following additional adverse events have been reported during the commercial use of AVAXIM. These events have been very rarely reported, however exact incidence rates are not known (cannot be estimated from the available data).
Nervous system disorders
Vasovagal syncope in response to injection
Skin and subcutaneous tissue disorders
Urticaria, rashes associated or not with pruritus

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.
Any suspected adverse events should be reported to the Ministry of Health (www.health.gov.il) according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9. Overdose

A few cases of overdose have been reported with AVAXIM, without specific adverse event.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Viral vaccine, ATC Code: J07BC02

AVAXIM 160 U confers immunity against hepatitis A virus by inducing antibody titres greater than those obtained after passive immunisation with immunoglobulin. Antibody appears shortly after the first injection and 14 days after vaccination more than 90% of immunocompetent subjects are seroprotected (titre above 20 mIU/millilitre).

One month after the first injection, almost 100% of subjects have antibody titres above 20mIU/millilitre. Serological data show continuing protection against hepatitis A for up to 36 months in subjects who responded to the first dose. In a study of 103 healthy adults who were followed serologically for three years after the first injection of AVAXIM, 99% still had at least 20 mIU/ml anti-HAV antibody at month 36.

The long-term persistence of protective antibody levels to hepatitis A virus after a second dose (booster) of AVAXIM 160 U has not been fully evaluated. Nevertheless, available data (antibody titres obtained two years after the second dose) suggest that anti-HAV antibodies persist beyond 10 years after the second dose in healthy individuals.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of acute toxicity, repeated dose toxicity, local tolerance and hypersensitivity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

2-phenoxyethanol
Ethanol anhydrous
Formaldehyde
Medium 199 Hanks *
Water for injections
Polysorbate 80
Hydrochloric acid and sodium hydroxide for pH adjustment
*Medium 199 Hanks (without phenol red) is a complex mixture of amino acids (including phenylalanine), mineral salts, vitamins and other components.

6.2. Incompatibilities

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

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze. If frozen, the vaccine should be discarded.

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

6.5. Nature and contents of container

0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger-stopper (bromochlorobutyl or chlorobutyl or bromobutyl) and attached needle and needle-shield.
0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger-stopper (bromochlorobutyl or chlorobutyl or bromobutyl), without needle.
Packs of 1, 5, 10 and 20 syringes.
0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger-stopper (bromochlorobutyl or chlorobutyl or bromobutyl), with 1 or 2 separate needles (for each syringe).
Packs of 1 and 10 syringes.
Not all pack sizes and presentations may be marketed.

6.6. Special precautions for disposal and other handling

For needle free syringes, the needle should be pushed firmly on to the end of the pre-filled syringe and rotated through 90 degrees.
Shake before injection to obtain a homogeneous suspension. The vaccine should be visually inspected before administration for any foreign particulate matter.

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

7. MANUFACTURER:

SANOFI PASTEUR France ,2

14 Espace Henry Vallée 69007 Lyon, France

8. LICENSE HOLDER

Medici Medical Ltd., 3 Hamachshev St., Netanya 4250713

9. MARKETING AUTHORISATION NUMBERS

110-46-29236-00

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