1 Elements for a Public Summary

1.1 Overview of disease epidemiology

Hepatitis A is a liver disease caused by the hepatitis A virus (HAV), mostly transmitted through fecal-oral route (1). Hepatitis A infection does not cause chronic liver disease and is rarely fatal.

Occurrence of a symptomatic infection increases progressively with age; while a large proportion of children would not develop symptoms, most adults will undergo mild disease in most cases. Manifestations of the disease can include fever, malaise, loss of appetite, diarrhea, nausea, abdominal discomfort and jaundice. No specific treatment is currently available for hepatitis A infected patients.

More than 126 million HAV infections and about 35,245 deaths from hepatitis A occurred in 2010 (2). Countries with low level of hygiene and sanitation are the most at risk. Paradoxically, a transition from high to intermediate prevalence may lead to an increase of the burden, which raises the interest of vaccination.

1.2 Summary of vaccine benefits

Immunogenicity of the vaccine has been demonstrated by 37 immunogenicity clinical trials performed in 20 different countries between 1991 and 2001 conducted in adults (16 years of age and over), children (12 months to 17 years) and infants (≤12 months), compiled by Vidor et al. (3). When given in a two-dose schedule with an interval of six months between doses, more than 95% of subjects were protected against hepatitis A disease within 14 days, and 100% within 28 days of the first dose, as defined by titers greater than 20 mIU/mL, (4) (5) (6) (7) (8) (9) (10) (11). A large-scale study took place in Russia (1996 to 2003) and measured the effectiveness of a single dose of Avaxim 160U formulation by comparing hepatitis A incidence before and after the vaccination of military personnel based in an endemic conflict area experiencing very high level of HAV transmission. 30,000 conscripted servicemen received one dose Avaxim 160U since 2000. There were no cases after a single dose in units in an endemic region where the coverage rate was 100%. In one unit where vaccination coverage was >80%, effectiveness of Avaxim 160U vaccine was 94.8%-98%. Overall, hepatitis A incidence decreased by 3.2 times (0.52 per 1,000), and by 10.2 times (0.43 per 1,000) in the conflict area (12) (13).

1.3 Unknowns relating to vaccine benefits

Avaxim 80U is not licensed for infants under 12 months of age, therefore this remains an area where the benefit of Sanofi Pasteur's Hepatitis A vaccination is still unknown.

In addition, literature is scarce to fully document the durability of protective immunity among immunocompromised patients, and the precise time schedule for vaccination needs to be established in future studies in this population.

1.4 Summary of safety concerns

Important identified risks: None

Important potential risks: None

Table 1: Missing information

Risk	What is known
Pregnant and breast feeding women	Data on the use of Avaxim160U or Avaxim80U in pregnant woman is limited. The vaccine should be given to a pregnant woman only if clearly needed (ask your doctor for advice). At the time being, no problem has been seen on available data on the use of Avaxim 160U during pregnancy. Data on the use of this vaccine in lactating women is limited. Therefore caution must be exercised when Avaxim 160 or Avaxim 80U is administered in a nursing mother. However, there is no anticipated safety concern.
Patients with lowered immunity either due to their medical history or to concomitant medication	Information on the use of hepatitis A vaccines in patients with lowered immunity is limited. The vaccine may not protect as well as it protects people whose immune system is healthy. If possible, vaccination should be postponed until the end of such disease or treatment. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV is recommended even if the antibody response might be limited.
Patients with chronic liver disease	Information on the use of hepatitis A vaccines in patients with chronic liver disease is limited. However these patients are at higher risk of severe Hepatitis A disease and no safety concern is anticipated.

1.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This vaccine has no additional risk minimization measure.

1.6 Planned post-authorization development plan

Not applicable

1.7 Summary of changes to the Risk Management Plan over time

Table 2: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 2.0 (DLP 31 May 2017)	November 2017	Based on MHRA recommendation in AR of RMP v1.0 -Risk of vasovagal syncope was deleted -Missing information update: 'rare adverse events that could not be identified during clinical trials' and 'data in patients of different racial and / or ethnic origin' were deleted 'Patients with chronic liver diseases' were added	RMP update follows the MHRA assessment report (AR) of RMP v1.0