Approval Date: October 23, 2020

Product: VAQTA

Proper Name: Hepatitis A Vaccine, Inactivated

Manufacturer: Merck Sharp & Dohme Corp.

Indication: For the prevention of disease cause by hepatitis A virus (HAV) in persons 12 months of age and older.

Description: VAQTA is an inactivated whole virus vaccine derived from hepatitis A virus grown in cell culture in human MRC-5 diploid fibroblasts.

BLA: BL 103606

Regulatory Milestone:

VAQTA is a vaccine indicated for active immunization against disease caused by hepatitis A virus (HAV) for persons ≥ 12 months of age. VAQTA was initially licensed in persons ≥ 2 years of age in the Unites States (U.S.) in 1996. The protective efficacy and safety were evaluated in a randomized, double-blind, placebo-controlled (alum placebo) study involving 1037 susceptible healthy children and adolescents 2 through 16 years of age in a U.S. community with recurrent outbreaks of hepatitis A (Monroe Efficacy Study). In subjects who were initially seronegative for hepatitis A (presence of antibody to hepatitis A is considered a demonstration of protection against hepatitis A disease), the protective efficacy of a single dose of VAQTA against hepatitis A disease was 100%, with 21 cases occurring in the placebo group and zero in the VAQTA group. Duration of efficacy after two doses of VAQTA in a subset of subjects in the Monroe Efficacy Study has

been documented to be nine years. The age indication for VAQTA was extended to children as young as 12 months of age in 2005, based on demonstration of non-inferiority of immune response in children 12-23 months of age as compared to children 23-25 months of age (HAV-057), as well as comparability of safety profile in the two age groups. At the time the age indication was extended to children as young as 12 months of age (August 11, 2005), Merck agreed to evaluate the safety of administering two doses of VAQTA six months apart in an additional 3000 children 12 to 23 months of age. Three additional studies were specified as post-marketing commitment studies in that approval letter: 1) a study to evaluate the safety and immunogenicity of two doses of VAQTA in an additional 2260 subjects 12-23 months of age; 2) second study to evaluate the safety and immunogenicity of two doses of VAQTA when administered with or without pneumococcal 7-valent conjugate vaccine (diphtheria CRM 197 protein) [Prevnar] and measles, mumps, rubella, varicella vaccine [ProQuad]; and 3) a third study to evaluate safety and immunogenicity of VAQTA when administered with or without diphtheria, tetanus toxoids, and acellular pertussis vaccine, adsorbed, DTaP [Infanrix] and haemophilus influenza b conjugate vaccine (tetanus toxoid conjugate) [PedvaxHIB]. The first two studies were previously submitted to the VAQTA BLA in an efficacy supplement, and resulted in the addition of data to the package insert (PI) for additional safety data for administration of VAQTA in subjects 12-23 months of age as well as inclusion of data for coadministration of VAQTA with Prevnar and Varicella [ProQuad] in sBLA 103606.5374 (approved March 25, 2010). With this supplement, Merck submitted the third of three post-marketing commitment studies (HAV-068) to the BLA to provide safety and immunogenicity data which support coadministration of VAQTA with DTaP and Haemophilus influenza b, as well as to increase the total safety database for administration of two doses of VAQTA in children 12-23 months of age, thus satisfying all post-marketing commitments designated in the VAQTA approval letter of August 11, 2005. The second part of this supplement

includes pooled safety data from five studies (HAV043, HAV-057, HAV-066, HAV-067, and HAV-068), assessing safety and immunogenicity of VAQTA given with or without concomitant childhood vaccines in at least 3000 children in the second year of life. These pooled safety data were reviewed, and no safety signal was identified which would preclude continued administration of VAQTA to children as young as 12 months of age. All five studies in this supplement were conducted in the U.S.

PDUFA Goal Date: July 19, 2012

Package Insert: Package Insert - VAQTA

Summary Basis for Regulatory Approval: July 10, 2012 Summary Basis for Regulatory Action-VAQTA

European Public Assessment Report: No data

Advisory Committee:

There were no product-specific concerns that would have benefited from an advisory committee discussion.

NCT Numbers:

- NCT03351933
- NCT00244374
- NCT00197002
- NCT00197015
- NCT00197236
- NCT00709592
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- NCT00096785
- NCT00851890

EudraCT Numbers:

- 2008-000526-39
- 2014-000933-21
- 2011-004400-38

Publications:

- Werzberger, A., Mensch, B., Kuter, B., Brown, L., Lewis, J., Sitrin, R., Miller, W., Shouval, D., Wiens, B., & Calandra, G. (1992). A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *The New England journal of medicine*, *327*(7), 453–457. https://doi.org/10.1056/NEJM199208133270702
- Beran, J., Beutels, M., Levie, K., Van Damme, P., Dieussaert, I., Gillet, M., Van Hoecke, C., & Tornieporth, N. (2000). A single dose, combined vaccine against typhoid fever and hepatitis A: consistency, immunogenicity and reactogenicity. *Journal of travel medicine*, *7*(5), 246–252. https://doi.org/10.2310/7060.2000.00073
- Hornick, R., Tucker, R., Kaplan, K. M., Eves, K. A., Banerjee, D., Jensen, E., & Kuter, B. (2001). A randomized study of a flexible booster dosing regimen of VAQTA in adults: safety, tolerability, and immunogenicity. *Vaccine*, *19*(32), 4727–4731. https://doi.org/10.1016/s0264-410x(01)00224-9
- Maria Petrecz, Camilo J. Acosta, Stephanie O. Klopfer, Barbara J. Kuter, Michelle G. Goveia, Jon E. Stek, Florian P. Schödel & Andrew W. Lee (2019) Safety and immunogenicity of VAQTA® in children 12-to-23 months of age with and without administration of other US pediatric vaccines, Human Vaccines & Immunotherapeutics, 15:2, 426-432, DOI: 10.1080/21645515.2018.1530934
- Werzberger, A., Mensch, B., Nalin, D. R., & Kuter, B. J. (2002). Effectiveness of hepatitis A vaccine in a former frequently affected community: 9 years' followup after the Monroe field trial of VAQTA. *Vaccine*, *20*(13-14), 1699–1701. https://doi.org/10.1016/s0264-410x(02)00042-7