Approval Date: December 19, 2018

Product: HAVRIX

Proper Name: Hepatitis A Vaccine, Inactivated

Manufacturer: GlaxoSmithKline Biologicals

Indication: For active immunization against disease caused by hepatitis A virus (HAV) for persons 12 months of age and older.

Description: HAVRIX (Hepatitis A Vaccine) is a sterile suspension of inactivated virus for intramuscular administration. The virus (strain HM175) is propagated in MRC-5 human diploid cells.

BLA: BL 103475

Regulatory Milestone:

Havrix is a vaccine indicated for active immunization against disease caused by hepatitis A virus (HAV) for persons ≥ 12 months of age. Havrix was initially licensed in persons ≥ 2 years of age in the Unites States (U.S.) in 1995. The protective efficacy and safety were evaluated in a controlled study involving 40,119 children 1-16 years of age in Thailand at high risk for hepatitis infection. The presence of antibody to hepatitis A is considered a demonstration of protection against hepatitis A disease. The age indication 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-210). At the time the age indication was extended to children as young as 12 months of age (10/17/05), GSK agreed to

evaluate the safety of administering two doses of Havrix six months apart in at least 3000 children 12 to 23 months of age. Three coadministration studies were specified as post-marketing commitment studies in that approval letter: 1) a study to evaluate the safety and immunogenicity of Havrix when administered with or without pneumococcal 7-valent conjugate vaccine (diphtheria CRM 197 protein) [Prevnar]; 2) safety and immunogenicity of Havrix when administered with or without diphtheria, tetanus toxoids, and acellular pertussis vaccine, adsorbed [Infanrix] and haemophilus b conjugate vaccine (tetanus toxoid conjugate) [ActHIB]; and 3) the safety and immunogenicity of Havrix when administered with or without measles, mumps, and rubella vaccine (MMRII) and varicella vaccine (Varivax). The first two studies were previously submitted to the Havrix BLA as efficacy supplements, and resulted in the addition of data to the package insert (PI) for coadministration of Havrix with Prevnar (approved 3/26/08) , and addition of data to the PI for coadministration of Havrix with Infanrix and ActHIB (approved 10/1/09). With this supplement, GSK submitted the third of three post-marketing commitment studies (HAV-231) to the BLA to provide safety and immunogenicity data which support 4 coadministration of Havrix with MMRII and Varivax in children in the second year of life. The second part of this supplement includes pooled safety data from four studies (HAV210, HAV-220, HAV-232 and HAV-231), assessing safety and immunogenicity of Havrix given with or without concomitant childhood vaccines in at least 3000 children in the second year of life. These pooled safety data will be included in the package insert and will replace the individual safety data for each of the other three studies.

PDUFA Goal Date: July 24, 2011

Package Insert: Package Insert - Havrix

Summary Basis for Regulatory Approval: July 21, 2011 Summary Basis for Regulatory Action - Havrix

European Public Assessment Report:

Advisory Committee:

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

NCT Numbers:

- NCT02712359
- NCT03183492
- NCT00197236
- NCT02124785
- NCT02082639
- NCT00289757
- NCT00291876
- NCT01405677
- NCT00596271
- NCT01218308
- NCT00316706
- NCT00197249
- NCT01307436
- NCT01037114
- NCT00139113
- NCT01349829
- NCT00197015
- NCT01360970
- NCT01379937
- NCT01282216
- NCT01352793
- NCT01978093
- NCT00122681
- NCT01041573
- NCT00197002
- NCT00057330
- NCT01196026
- NCT01252680
- NCT00190242
- NCT03654677
- NCT03654664
- NCT01000324
- NCT00224484
- NCT02038907
- NCT00128661
- NCT00513409
- NCT03917654
- NCT00483470
- NCT00578175
- NCT01102296
- NCT02583412
- NCT01190215
- NCT00684671
- NCT02526550
- NCT00289731
- NCT00624819
- NCT00125047
- NCT00125008
- NCT00544271
- NCT01830855
- NCT02184572
- NCT00466947
- NCT01439360
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- NCT01159951
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- NCT01311024
- NCT03859687
- NCT00880893
- NCT00937950
- NCT02747407
- NCT01702428
- NCT00603252
- NCT01947465
- NCT00474526

EudraCT Numbers:

- 2005-003526-25
- 2015-001509-15
- 2015-001530-25
- 2013-003459-39
- 2007-006651-39
- 2013-001918-15
- 2004-004370-85
- 2009-014853-33
- 2015-005191-18

- 2009-014275-53
- 2013-001419-64
- 2011-004891-12
- 2015-001514-97
- 2004-000518-37
- 2008-006083-11
- 2011-004751-39
- 2004-001325-14
- 2012-003484-22
- 2010-020331-39
- 2011-004905-26
- 2008-000526-39
- 2011-001333-17
- 2017-000454-18
- 2009-016773-15
- 2009-015198-11
- 2011-000758-41
- 2010-023873-20
- 2009-015588-15
- 2011-006161-18
- 2008-005149-48
- 2011-002076-16
- 2010-020330-26
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- 2009-016055-22
- 2016-004904-74
- 2013-002451-15
- 2019-001186-33
- 2015-001449-93
- 2011-005860-31
- 2017-001071-23
- 2007-005392-34

Publications:

- Van Herck, K., & Van Damme, P. (2005). Prevention of hepatitis A by Havrix: a review. *Expert review of vaccines*, *4*(4), 459–471. https://doi.org/10.1586/14760584.4.4.459
- Bradley A. Connor, John Phair, David Sack, David McEniry, Richard Hornick, Dalfoni Banerjee, Erin Jensen, Barbara Kuter, Randomized, Double-Blind Study in Healthy Adults to Assess the Boosting Effect of Vaqta or Havrix after a Single Dose of Havrix, *Clinical Infectious Diseases*, Volume 32, Issue 3, 1 February 2001, Pages 396–401, https://doi.org/10.1086/318522
- Connor, B. A., Phair, J., Sack, D., McEniry, D., Hornick, R., Banerjee, D., Jensen, E., & Kuter, B. (2001). Randomized, double-blind study in healthy adults to assess the boosting effect of Vaqta or Havrix after a single dose of Havrix. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *32*(3), 396–401. https://doi.org/10.1086/318522
- Koen Van Herck & Pierre Van Damme (2005) Prevention of hepatitis A by Havrix™: a review, Expert Review of Vaccines, 4:4, 459-471, DOI: 10.1586/14760584.4.4.459
- Yu, C., Song, Y., Qi, Y., Li, C., Jiang, Z., Li, C., Zhang, W., Wang, L., & Xia, J. (2016). Comparison of immunogenicity and persistence between inactivated hepatitis A vaccine Healive® and Havrix® among children: A 5-year follow-up study. *Human vaccines & immunotherapeutics*, *12*(10), 2595–2602. https://doi.org/10.1080/21645515.2016.1197450

- Ostergaard, L., Lucksinger, G. H., Absalon, J., Beeslaar, J., Eiden, J., Jansen, K. U., York, L. J., Quinn, A., Graversen, M. E., & Perez, J. L. (2016). A phase 3, randomized, active-controlled study to assess the safety and tolerability of meningococcal serogroup B vaccine bivalent rLP2086 in healthy adolescents and young adults. *Vaccine*, *34*(12), 1465–1471. https://doi.org/10.1016/j.vaccine.2016.01.044
- Theeten, H., Van Herck, K., Van Der Meeren, O., Crasta, P., Van Damme, P., & Hens, N. (2015). Long-term antibody persistence after vaccination with a 2-dose Havrix (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions. *Vaccine*, *33*(42), 5723–5727. https://doi.org/10.1016/j.vaccine.2015.07.008