Approval Date: August 20, 2020

Product: GARDASIL 9

Proper Name: Human Papillomavirus 9-valent Vaccine, Recombinant

Manufacturer: Merck Sharp & Dohme Corp.

Indication:

- Indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:
    - Cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58.
    - Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
- And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
    - Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS).
    - Cervical intraepithelial neoplasia (CIN) grade 1.
    - Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3.
    - Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3.
    - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.
- Indicated in boys and men 9 through 45 years of age for the prevention of the following diseases:

  - Anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
  - Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
- And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
  - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

Description: GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

BLA: 125508

Regulatory Milestone:

Merck's first licensed HPV vaccine, GARDASIL, was approved in June 2006. Prevention of vaginal and vulvar cancers in women was added to the indication in 2008 (STN 125126/419), use in males and prevention of genital warts were added to the indication in 2009 (STN 125126/1297), and prevention of anal cancer and AIN in men and women was added to the indications and usage in 2010 (STN 125126/1895). In 2014, GARDASIL 9 was licensed with indications to prevent diseases related to the HPV types covered by the vaccine in girls and women 9 through 26 years of age, and boys 9 through 15 years of age. In 2015, the GARDASIL 9 indications applicable to males were extended to include men 16 through 26 years of age (STN 125508/15).

PDUFA Goal Date: October 6, 2018

Package Insert: Package Insert - GARDASIL 9

Summary Basis for Regulatory Approval: October 5, 2018 Summary Basis of Regulatory Action - GARDASIL 9

European Public Assessment Report: Human medicine European public assessment report (EPAR): Gardasil 9

Advisory Committee:

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting because review of this supplemental application did not identify concerns or issues which would have benefitted from an advisory committee discussion.

Safety:

Unsolicited adverse events (AEs), serious adverse events (SAEs), new medical conditions, and deaths were monitored for a total of 10 years in the studies of GARDASIL in women 27 through 45 years of age (studies V501-019 and V501-019-21). Solicited AEs were not collected due to the extensive safety database of GARDASIL in younger age groups. The safety profile of GARDASIL in 24- through 45-year-old women was not notably different from what has been characterized in younger women. Based on safety data for GARDASIL and GARDASIL 9 in women 16 through 26 years of age (study V503-001, reviewed under STN 125508/0), the only difference anticipated is slightly higher rates of local reactogenicity with GARDASIL 9 compared with GARDASIL. Therefore, the safety of GARDASIL 9 for women and men 27 through 45 years of age can be extrapolated from cross-study comparisons in younger ages and across GARDASIL and GARDASIL 9 formulations.

NCT Numbers:

- NCT02567955
- NCT03431246
- NCT03023631
- NCT03525210
- NCT03979014
- NCT03943875
- NCT03546842
- NCT04206813
- NCT02968420
- NCT03519464
- NCT03451071
- NCT03158220
- NCT04430907
- NCT01824537
- NCT04274153
- NCT03848039
- NCT03350698
- NCT03947775
- NCT03391921
- NCT03675256
- NCT03626467
- NCT04688476
- NCT04436133
- NCT03180034
- NCT04459221
- NCT02568566
- NCT02834637
- NCT03036930
- NCT03832049
- NCT04199689
- NCT04270773
- NCT01492582
- NCT04635423
- NCT03284866
- NCT04235257
- NCT04255849
- NCT04265950
- NCT04490018
- NCT03051516
- NCT03542227
- NCT01245764
- NCT03493542
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- NCT01462357
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- NCT01047345
- NCT04422366
- NCT00157950
- NCT04425291
- NCT00496626
- NCT03998254
- NCT02576054
- NCT04508309
- NCT00786409
- NCT02993757
- NCT00806676
- NCT03123419
- NCT00380367
- NCT00092547
- NCT04453241
- NCT01096134
- NCT00635830
- NCT00524745
- NCT01456715
- NCT03083249
- NCT00543543
- NCT01101750
- NCT01914367
- NCT00727636
- NCT01427777
- NCT01062074
- NCT00501137
- NCT03296397
- NCT01717118
- NCT00573651

EudraCT Numbers:

- 2019-003135-36
- 2020-002332-73
- 2014-005717-23
- 2014-004581-16
- 2018-004662-33
- 2013-002340-90
- 2016-002083-13
- 2007-003528-39
- 2010-023393-39
- 2012-004007-13
- 2017-000110-35
- 2017-001205-33
- 2009-015500-26
- 2015-005093-38
- 2013-003399-10
- 2015-002932-42
- 2017-000108-42
- 2011-006002-27
- 2013-002951-14
- 2012-000445-12
- 2017-000111-16

- 2013-002009-70
- 2004-002945-10
- 2018-002764-94
- 2017-004322-15
- 2015-004524-65
- 2019-003486-17
- 2018-000215-24
- 2019-003236-23
- 2017-000112-42
- 2015-004212-37
- 2014-003177-42
- 2011-002035-26
- 2019-001153-10
- 2013-001314-15
- 2009-011617-25

Publications:

- Schilling, A., Parra, M. M., Gutierrez, M., Restrepo, J., Ucros, S., Herrera, T., Engel, E., Huicho, L., Shew, M., Maansson, R., Caldwell, N., Luxembourg, A., & Ter Meulen, A. S. (2015). Coadministration of a 9-Valent Human Papillomavirus Vaccine With Meningococcal and Tdap Vaccines. *Pediatrics*, *136*(3), e563–e572. https://doi.org/10.1542/peds.2014-4199
- Finney Rutten, L. J., Radecki Breitkopf, C., St Sauver, J. L., Croghan, I. T., Jacobson, D. J., Wilson, P. M., Herrin, J., & Jacobson, R. M. (2018). Evaluating the impact of multilevel evidence-based implementation strategies to enhance provider recommendation on human papillomavirus vaccination rates among an empaneled primary care patient population: a study protocol for a stepped-wedge cluster randomized trial. *Implementation science : IS*, *13*(1), 96. https://doi.org/10.1186/s13012-018-0778-x
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- Stankiewicz Karita, H. C., Hauge, K., Magaret, A., Mao, C., Schouten, J., Grieco, V., Xi, L. F., Galloway, D. A., Madeleine, M. M., & Wald, A. (2019). Effect of Human Papillomavirus Vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA): A Trial Protocol. *JAMA network open*, *2*(4), e190819. https://doi.org/10.1001/jamanetworkopen.2019.0819
- Mboumba Bouassa, R. S., Nodjikouambaye, Z. A., Sadjoli, D., Adawaye, C., Péré, H., Veyer, D., Matta, M., Robin, L., Tonen-Wolyec, S., Moussa, A. M., Koyalta, D., & Belec, L. (2019). High prevalence of cervical high-risk human papillomavirus infection mostly

covered by Gardasil-9 prophylactic vaccine in adult women living in N'Djamena, Chad. *PloS one*, *14*(6), e0217486. https://doi.org/10.1371/journal.pone.0217486