Approval Date: September 15, 2020

Product: Proquad

Proper Name: Measles, Mumps, Rubella and Varicella Virus Vaccine Live

Manufacturer: Merck Sharpe & Dohme Corp

Indication: Active immunization for the prevention of measles, mumps, rubella, and varicella in individuals 12 months through 12 years of age.

Description: ProQuad (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) is a combined, attenuated, live virus vaccine containing measles, mumps, rubella, and varicella viruses.

BLA: 125108

Regulatory Milestone:

Merck proposed plans for implementation of the process in the manufacturing of in order to Merck's in a Type C meeting briefing package submitted on November 1, 2013. In written feedback dated November 22, 2013, CBER agreed with analytical comparability plan, the filing strategy, and the design of the proposed VARIVAX clinical study (V210-063) to assess the safety and immunogenicity of the vaccine manufactured with the virus. Merck agreed with CBER's recommendations in written feedback dated on December 2, 2013.

PDUFA Goal Date: March 16, 2017

Package Insert:

- Package Insert - Refrigerator-Stable Formulation - ProQuad

- Package Insert - Frozen Formulation - Recombinant Human Albumin (RHA) - ProQuad
- Package Insert - Frozen Formulation - Human SerumAlbumin (HSA) - ProQuad

Summary Basis for Regulatory Approval: March 15, 2017 Summary Basis for Regulatory Action - ProQuad

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

Advisory Committee:

A Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meeting was not held as there were no issues or concerns that presented during the course of review of the supplement that required consult from the advisory committee.

Safety:

All subjects were followed for safety (daily temperatures, injection-site adverse events, and systemic adverse events) for 42 days after each vaccination. All subjects were followed for serious adverse events from the time of enrollment until the end of the study. In addition, medically-attended events were collected through 180 days after completing the 42-day safety follow-up post Dose 2. Although no formal hypothesis was tested regarding safety, a summary of safety results following each dose of vaccine demonstrated that the safety profile of the two vaccines was similar. Overall, the two vaccination groups were comparable in terms of the incidence rates of adverse events overall, systemic adverse events, injection-site adverse events, vaccine-related adverse events, and serious adverse events.

NCT Numbers:

- NCT02687763
- NCT00560755
- NCT00402831
- NCT00566527
- NCT00432042
- NCT00986232
- NCT00985153
- NCT00839917
- NCT00985166
- NCT00578175
- NCT00984295
- NCT00975507
- NCT00326183
- NCT00312858
- NCT02712203
- NCT00109343
- NCT00370227
- NCT01536405
- NCT00626327
- NCT01341639
- NCT00406211
- NCT01506193
- NCT00474266
- NCT00969436
- NCT00384397
- NCT00483574
- NCT00422292
- NCT01621802
- NCT00258726
- NCT01738841
- NCT00373958
- NCT00871000
- NCT00847145
- NCT00474526
- NCT02712177

EudraCT Numbers:

- 2007-002468-88
- 2017-000454-18
- 2014-004694-16
- 2007-002438-12
- 2006-004129-27
- 2017-001443-13
- 2010-021490-37
- 2011-004638-32

Publications:

- Ferrera, G., Cuccia, M., Mereu, G., Icardi, G., Bona, G., Esposito, S., Marchetti, F., Messier, M., Kuriyakose, S., & Hardt, K. (2012). Booster vaccination of pre-school children with reduced-antigen-content diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine co-administered with measles-mumps-rubella-varicella vaccine: a randomized, controlled trial in children primed according to a 2 + 1 schedule in infancy. *Human vaccines & immunotherapeutics*, *8*(3), 355–362. https://doi.org/10.4161/hv.18650
- Huang, L. M., Lee, B. W., Chan, P. C., Povey, M., & Henry, O. (2013). Immunogenicity and safety of combined measles-mumps-rubella-varicella vaccine using new measles and rubella working seeds in healthy children in Taiwan and Singapore: a phase II, randomized, double-blind trial. *Human vaccines & immunotherapeutics*, *9*(6), 1308–1315. https://doi.org/10.4161/hv.24035
- Yetman, R. J., Shepard, J. S., Duke, A., Stek, J. E., Petrecz, M., Klopfer, S. O., Kuter, B. J., Schödel, F. P., & Lee, A. W. (2013). Concomitant administration of hepatitis A vaccine with measles/mumps/rubella/varicella and pneumococcal vaccines in healthy 12- to 23-month-old

children. *Human vaccines & immunotherapeutics*, *9*(8), 1691–1697. https://doi.org/10.4161/hv.24873

- Lalwani, S., Chatterjee, S., Balasubramanian, S., Bavdekar, A., Mehta, S., Datta, S., Povey, M., & Henry, O. (2015). Immunogenicity and safety of early vaccination with two doses of a combined measles-mumps-rubella-varicella vaccine in healthy Indian children from 9 months of age: a phase III, randomised, non-inferiority trial. *BMJ open*, *5*(9), e007202. https://doi.org/10.1136/bmjopen-2014-007202
- Marshall, G. S., Senders, S. D., Shepard, J., Twiggs, J. D., Gardner, J., Hille, D., Hartzel, J., Valenzuela, R., Stek, J. E., & Helmond, F. A. (2016). A double blind, randomized, active controlled study to assess the safety, tolerability and immunogenicity of measles, mumps rubella, and varicella vaccine (MMRV) manufactured using an alternative process. *Human vaccines & immunotherapeutics*, *12*(8), 2188–2196. https://doi.org/10.1080/21645515.2016.1165374
- Henry, O., Brzostek, J., Czajka, H., Leviniene, G., Reshetko, O., Gasparini, R., Pazdiora, P., Plesca, D., Desole, M. G., Kevalas, R., Gabutti, G., Povey, M., & Innis, B. (2018). One or two doses of live varicella virus-containing vaccines: Efficacy, persistence of immune responses, and safety six years after administration in healthy children during their second year of life. *Vaccine*, *36*(3), 381–387. https://doi.org/10.1016/j.vaccine.2017.11.081
- Haas, H., Richard, P., Eymin, C., Fiquet, A., Kuter, B., & Soubeyrand, B. (2019). Immunogenicity and safety of intramuscular versus subcutaneous administration of a combined measles, mumps, rubella, and varicella vaccine to children 12 to 18 months of age. *Human vaccines & immunotherapeutics*, *15*(4), 778–785. https://doi.org/10.1080/21645515.2018.1549452
- Santos, E., Noronha, T. G., Alves, I. S., Cruz, R., Ferroco, C., Brum, R. C., Oliveira, P., Siqueira, M. M., Lima, M. C., Ramos, F., Bragagnolo, C. M., Camacho, L., & Maia, M. (2019). Immunogenicity and safety of the combined vaccine for measles, mumps, and rubella isolated or combined with the varicella component administered at 3-month intervals: randomised study. *Memorias do Instituto Oswaldo Cruz*, *114*, e180517. https://doi.org/10.1590/0074-02760180517
- Zafack, J. G., Bureau, A., Skowronski, D. M., & De Serres, G. (2019). Adverse events following immunisation with four-component meningococcal serogroup B vaccine

(4CMenB): interaction with co-administration of routine infant vaccines and risk of recurrence in European randomised controlled trials. *BMJ open*, *9*(5), e026953. https://doi.org/10.1136/bmjopen-2018-026953