

Summary Basis for Regulatory Action

Date: February 22, 2017

From: Luba Vujcic, Chair of the Review Committee

BLA/ STN#: 125122/1309

Applicant Name: Merck, Sharp & Dohme Corp.

Date of Submission: April 25, 2016

Goal Date: February 23, 2017

Proprietary Name/ Established Name: RotaTeq®/Rotavirus Vaccine, Live, Oral, Pentavalent

Current Indication: Rotateq® is indicated for the prevention of rotavirus gastroenteritis caused by the G1, G2, G3, and G4 serotypes contained in the vaccine. Rotateq® is approved for use in infants 6 weeks to 32 weeks of age.

Proposed New Indication: RotaTeq® is a vaccine indicated for the prevention of rotavirus gastroenteritis caused by types G1, G2, G3, G4, and G9.

Recommended Action:

The Review Committee recommends approval of this clinical efficacy supplement to include an indication that has been revised as follows: RotaTeq® is a vaccine indicated for the prevention of rotavirus gastroenteritis caused by types G1, G2, G3, G4, and G9. We also recommend approval of revisions to the package insert labeling to comply with the 2014 Final Rule, *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*.

Review Office Signatory Authority: Wellington Sun, MD, Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

I concur with the summary review.

I concur with the summary review and include a separate review to add further analysis.

I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA.

Document title	Reviewer name, Document date
Clinical Review • <i>Clinical (OVRP/DVRPA)</i>	Gueorgui Dubrocq, MD
Statistical Reviews • <i>Clinical data</i> • <i>Non-clinical data</i>	Mridul Chowdhury, Ph.D. Yin (Charles) Cheung, Ph.D.
CMC Reviews • <i>CMC (OVRP/DVRPA)</i>	Dino Feigelstock, Ph.D.

1. Introduction

RotaTeq was granted approval by the FDA on February 6, 2006, for the prevention of rotavirus gastroenteritis in infants and children caused by the types G1, G2, G3, and G4 when administered as a 3-dose series to infants between the ages of 6 to 32 weeks. Studies performed for licensure proved that the vaccine is safe and effective and does not cause intussusception. In this Clinical Efficacy Supplement to their Biologics License Application (sBLA), Merck, Sharp & Dohme Corp., Inc (hereafter referred to as Merck) submitted additional clinical data to support the additional approval of Rotavirus Vaccine, Live, Oral, Pentavalent (RotaTeq) for the prevention of rotavirus gastroenteritis caused by type G9 when administered as a 3 dose series to infants between the ages of 6 and 32 weeks. Efficacy of the G9P1A[8] type of RotaTeq in infants 6 to 32 weeks of age was evaluated in three clinical studies, Protocols 006 and 007, which were the efficacy studies previously conducted in support of original US licensure, and a new Japanese efficacy study, Protocol 029.

2. Background

Rotavirus infection is the leading cause of severe gastroenteritis among infants and young children worldwide. Prior to the introduction of rotavirus vaccine in the United States in 2006, rotavirus infection caused significant morbidity among U.S. children. Although most rotavirus infections occur in the first and second years of life, the age group at greatest risk of severe gastroenteritis includes children 4 to 23 months of age and subsequent infections usually result in much milder disease. In the US, rotaviruses containing six distinct P and G combinations that are most prevalent include G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and G9P[6]. Worldwide regional G9P[8] prevalence ranges from 7 to 16% and the G9 type isolated from humans, although in rare prevalence, has also been associated with P[4], P[6], P[9], P[10], P[11], and P[19]. While there are regional variations, the literature suggests that globally approximately 90% of G9 is associated with P[8].

RotaTeq is a live, oral, pentavalent vaccine which contains a combination of 5 human-bovine (WC3) reassortant rotavirus strains (WI79-9, SC2-9, WI78-8, BrB-9, and WI79-4, designated as G1, G2, G3, G4, and P1A[8]). All reassortants

are composed of the bovine rotavirus strain WC3 (Wistar Calf 3) genome background. The drug substance used to prepare the drug product is a (b) (4) [REDACTED]. Each dose of RotaTeq consists of a 2mL, oral solution of 5 live human-bovine reassortant rotaviruses, which contains a minimum of 2.0 to 2.8 x 10⁶ infectious units (IU) per reassortant dose, depending on the serotype, and not greater than 116 x 10⁶ IU per aggregate dose.

In the original submission, efficacy was analyzed by serotype, based on VP7 (G) typing assays (including typing for G9) for stool specimens collected in studies 006 and 007. A VP4 (P) typing assay was developed and validated after licensure, and stools from studies 006 and 007 were analyzed retrospectively. The validation reports demonstrated accuracy and precision for determining types G1, G2, G3, G4, G5, and G9 using the VP7 assay and P1a, (b) (4) [REDACTED] using the VP4 assay. The Applicant submitted the results of the analyses for P types, in addition to a post hoc analysis of health care utilization data, in a BLA supplement designated as STN 125122/201. The request to include prevention of rotavirus gastroenteritis caused by type G9P1A[8] in the indication was not granted on September 28, 2007, due to a low number of cases and because there were studies in which the endpoints and analyses for P types were not pre-specified. However, these data supporting the G9P1A[8] type were briefly described in section 14 (Clinical Studies) of the package insert.

During a Type C meeting held in June, 2015, Merck proposed combining data from a more recent analysis of samples from the studies previously used to support licensure in the United States (studies 006 and 007) with data from a new efficacy and safety study conducted in Japan (study 029), which was designed to prospectively assess the efficacy of rotavirus gastroenteritis including G9P1A[8], to extend the indication for prevention of rotavirus gastroenteritis caused by G type containing P1A[8], e.g., type G9. During the meeting, CBER indicated that review of the data from study 029 was needed before any decision could be made regarding the proposed expanded indication.

3. Clinical/Statistical/Pharmacovigilance

a) Clinical Program

Efficacy of Rotateq in the prevention of rotavirus gastroenteritis caused by type G9P1A[8] in infants 6 to 32 weeks of age was evaluated in three clinical studies (029, 006, 007). The data from these studies support the effectiveness of RotaTeq against rotavirus gastroenteritis caused by G9 associated with P1A[8].

Efficacy data for G9P1A[8] evaluation in studies 006 and 007 is post-hoc as these studies were part of the original licensure (and the assay used for the evaluation of P types had not been validated prior to the original licensure). Study 029 was a phase 3 randomized, multicenter, double

blind, placebo controlled, parallel group comparison study trial to evaluate the safety and immunogenicity of RotaTeq in healthy Japanese infants aged 6 to 12 weeks after birth. The subjects were randomized (1:1) to receive either RotaTeq or placebo. Study 006 was a phase 3 double-blinded, randomized, placebo-controlled, international multicenter study to evaluate the efficacy, immunogenicity and safety of RotaTeq. Study 007 evaluated the efficacy of RotaTeq at end expiry potency.

The primary objective of the Japanese study 029 was to demonstrate the efficacy of a 3 dose regimen of RotaTeq against naturally occurring rotavirus gastroenteritis of any severity caused by rotavirus serotypes G9P1A[8], in addition to the currently indicated G1, G2, G3, and G4 serotypes, occurring at least 14 days following the third dose in healthy infants. A total of 6,329 subjects aged 6 to 12 months of age were included in the evaluable (per-protocol) efficacy populations.

In Study 029, RotaTeq was shown to prevent rotavirus gastroenteritis caused by G1, G2, G3 and G4 types and G-types associated with type P1A[8] (e.g., G9); the vaccine efficacy was 74.5% (95% CI: 39.9, 90.6). G9P1A[8]-associated gastroenteritis was observed in 0/356 and 5/354 subjects in the RotaTeq and placebo groups, respectively (100% [95% CI: -9.0, 100]). In studies 006 and 007, additional cases of G9P1A[8]-associated gastroenteritis were identified retrospectively, and occurred less frequently in the RotaTeq group than the placebo group. The data in this submission support that rotavirus gastroenteritis due to G9, when associated with P1A[8], can be prevented by RotaTeq. The review team proposed revising the reference to P1A[8] in the package insert to G9P1A[8] since all of the types were associated with P1A[8]. Also, instead of referring to G9P1A[8], G1, G2, G3, and G4 as serotypes, they are referred to “types”, since G9P1A[8] is not a serotype.

The Applicant’s analysis of the pooled data of the G9P1A[8] cases was a post hoc analysis combining the data from pre-licensure studies 006 and 007 with new data from study 029. For efficacy based on Protocol 029 alone, the vaccine efficacy for RotaTeq against rotavirus gastroenteritis, regardless of severity, due to all reported serotypes was 74.5% (95% CI: 39.9%, 90.6%). For serotype G9P1A[8], the VE estimate was 100% with lower confidence bound -9.0%, a value relatively closer to zero than the negative lower bounds for other G-serotypes included in the pre-licensure studies. Efficacy trials are not typically powered for serotype-specific efficacy. The data in this sBLA indicate efficacy with respect to type G9 which all contained P1A[8].

b) Pediatrics

Currently, RotaTeq is approved in infants 6 to 32 weeks of age for the prevention of rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4. The safety and effectiveness of RotaTeq have not been established in infants less than 6 weeks of age or greater than 32 weeks of age. Data are available from clinical studies to support the use of RotaTeq in pre-term infants according to their age in weeks since birth and the use in infants with controlled gastroesophageal reflux disease.

The Pediatric Research Equity Act (PREA) applies to this supplement since it is for a new indication to include prevention of rotavirus gastroenteritis caused by type G9P1A[8]. PeRC agreed to a partial waiver in pediatric subjects 0 to less than 6 weeks of age, and greater than 32 weeks to less than 17 years of age because the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric age groups. PeRC also agreed that RotaTeq has now been fully assessed in patients 6 weeks to 32 weeks of age, and that waivers can be granted for patients < 6 weeks of age and >32 weeks of age.

c) Other Special Populations

No other special populations were evaluated. This product is only intended for use in infants 6 to 32 weeks of age.

4. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The product in this supplement has not changed from the original product. On June 23, 2016, we requested the SOPs and the validation studies for the VP7 fecal PCR assay (used to detect serotypes G1, G2, G3, and G4, as well as G9) and the VP4 fecal PCR assay (used to detect P1A[8]). The Applicant submitted the requested information to this supplement on August 19, 2016.

The SOP and validation studies conducted on the Rotavirus VP4 PCR-Serotyping assay were previously reviewed under the submission designated STN 125122/201 and found to be acceptable. The VP7 assay was previously reviewed during the IND phase; however, the product reviewer assigned to this supplement reviewed again the assay data provided under this supplement. Review of the validation of the Rotavirus VP7 PCR-serotyping assay was performed which assessed the ruggedness, precision and accuracy of the assay, and the limit of detection (LOD). Review of the validation results showed that the assay was valid for its intended use.

b) CBER Lot Release (only applicable for BLAs)

N/A

c) Facilities review/inspection

N/A

d) Environmental Assessment

N/A

e) Product Comparability

N/A

5. Nonclinical Pharmacology/Toxicology

N/A

6. Clinical Pharmacology

N/A

7. Safety

Safety data from Study 029 were reviewed in this sBLA; safety data in study 006 and 007 were previously reviewed as part of BLA (STN 125122/0) for licensure in 2006. The safety evaluation in Study 029 included assessments of solicited adverse events (AEs), unsolicited AEs, and serious adverse events (SAEs). A total of 761 subjects were included in the safety populations from Study 029. The rates and severities of solicited adverse reactions were comparable between RotaTeq and placebo groups. The most frequent solicited adverse reaction reported after any vaccination within 7 days was fever (25% in the RotaTeq group, 27% in the placebo group), followed by diarrhea (10% in each group) and vomiting (7% in each group).

There were no reported cases of intussusception in either group. One subject died in the RotaTeq group ^{(b) (6)} days after receiving the second dose due to complications of respiratory syncytial virus bronchiolitis and the clinical reviewer agreed that the event did not appear to be related to the study vaccine. The number of serious adverse events appeared comparable between both groups (8 in the RotaTeq group and 10 in the placebo group), and none appeared to have a causal relationship to the vaccine.

There are no new safety concerns since the product has not changed and the safety data from the new Study 029 were consistent with the previously

submitted safety data. Thus, the Applicant's plan to monitor for unanticipated safety issues via routine pharmacovigilance is acceptable and no post-marketing commitments are required.

8. Advisory Committee Meeting

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

9. Other Relevant Regulatory Issues

There are no additional relevant regulatory issues.

10. Labeling

CBER communicated with the Applicant to achieve consistency with CBER's current guidance on the intent and format of package inserts. The label indication in the package insert was finalized to add "prevention of rotavirus gastroenteritis caused by type G9" for consistency with prior approvals for this product and for other rotavirus vaccines. These changes can be seen in the Highlights section and in the Full Prescribing Information (in the Indications and Usage, Dosage Forms and Strengths, and Clinical Trials with most edits in Section 14.5, Rotavirus Gastroenteritis by Type). Also, small edits were made throughout the label to change "serotype" to "type" and to change "REST" to Study 006. In addition, important revisions to the label included updates to section 8 to comply with the 2014 Final Rule, *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, also known as the Pregnancy and Lactation Labeling Rule (PLLR). All issues were resolved after exchange of information and discussions with Merck. The final draft label was received on February 14, 2017, reviewed by the clinical team and review committee, and found to be acceptable.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The data submitted to this sBLA provide evidence to support the safety and effectiveness of three doses of RotaTeq in infants 6 to 32 weeks of age for the prevention of rotavirus gastroenteritis caused by the G9P1A[8] type. The label indication in the package insert was finalized to add "prevention of rotavirus gastroenteritis caused by type G9" for consistency with prior approvals for this product and for other rotavirus vaccines.

b) Risk/ Benefit Assessment

The overall risk-benefit of RotaTeq in infants 6 through 32 weeks of age continues to be favorable based on the observed efficacy and safety data submitted in this sBLA.

c) Recommendation for Postmarketing Activities

Clinical review of the data in this submission did not identify new safety concerns that would prompt the need for a post marketing study.