Unit: Technical Assessment Unit

Public assessment report for biological products

(RotaTeq®)

Administrative information:

Trade name of the medicinal product:	RotaTeq®
INN (or common name) of the active substance(s):	One dose (2 ml) contains rotavirus type*: G1 ≥ 2.2 x 10^6 IU[1] G2 ≥2.8 x 10^6 IU[1] G3 2.2 x 10^6 IU[1] G4 2.0 x 10^6 IU[1] P1A[8] 2.3 x 10^6 IU[1] * Human-bovine rotavirus reassortants (live), produced in Vero cell. 1 Infectious Units.
Manufacturer of the finished product	Merck Sharp & Dohme Corp. Sumneytown Pike P.O. Box 4 West Point, Pennsylvania, U.S. 19486-0004
Marketing Authorization holder	Merck sharp & Dohme Corp., asubidiary of merck &co., Inc,1 Merck Drive, P.o Box 100, Whitehouse Station, NJ 08889, US,License #0002.
Applied Indication(s):	RotaTeq is indicated for the active immunization of infants from the age of 6 weeks to 32 weeks for prevention of gastroenteritis due to rotavirus infection.
Pharmaceutical form(s) and strength(s):	Oral Solution Pale yellow clear liquid that may have a pink tint - One dose (2 ml) contains rotavirus type*: G1 ≥ 2.2 x 10^6 IU[1] G2 ≥2.8 x 10^6 IU[1] G3 2.2 x 10^6 IU[1] G4 2.0 x 10^6 IU[1] P1A[8] 2.3 x 10^6 IU[1]

	* Human-bovine rotavirus reassortants (live), produced in Vero cell. 1 Infectious Units.
Route of administration	oral administration only
Type of registration (EMA/FDA – Local)	EMA

List of abbreviations

DNA	Deoxyribonucleic acid.
EMA	European Medicines Agency
IU	International Unit
WHO	World Health Organization
IgA	Immunoglobulin A
G1	refers to a specific serotype (genotype) component within Rotavirus
G2	refers to a specific serotype (genotype) component within Rotavirus
G3	refers to a specific serotype (genotype) component within Rotavirus
G4	refers to a specific serotype (genotype) component within Rotavirus
G9	refers to a specific serotype(genotype) component within Rotavirus
GMT	geometric mean titre
SNA	Serum Neutralizing Antibody
RVGE	rotavirus gastroenteritis

Table of contents

1. General introduction about the product including brief description of the AI, its mode of action and indications.

- RotaTeq™ (Rotavirus Vaccine, Live, Oral, Pentavalent) is a combination of five monovalent vaccine bulks (redispensed virus fluids of G1, G2, G3, G4, and P1 reassortants) in a liquid formulation for oral administration. The calculated composition of the vaccine per 2 mL

dose is provided in MA file.

- The formulation for RotaTeq™ consists of 85% (v/v) stabilizer solution containing sucrose, sodium citrate, sodium phosphate, sodium hydroxide, and polysorbate-80. The remaining 15% (v/v) consists of re-dispensed virus fluids (G1, G2, G3, G4, and P1 reassortants in LPKM-3 culture medium) and Rotavirus Diluent, added in appropriate proportions to meet target potencies. The pH of the vaccine formulation is targeted to 6.0–6.7.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the general introduction

2.2.2 Drug Substance (Active ingredient)

- **General information**

Nomenclature:

- RotaTeq™ (Rotavirus Vaccine, Live, Oral, Pentavalent) is a combination of five live human bovine rotavirus reassortant strains (G1, G2, G3, G4, and P1) that belong to the group A rotaviruses.
- All five reassortant rotaviruses express desired serotype specificities that contain particular combinations of genome segments derived from each of the human and bovine parental rotavirus strains.

General properties:

- RotaTeq™ is a combination of five human-bovine reassortant rotavirus strains (designated as G1, G2, G3, G4, and P1) that belong to the group A rotaviruses. All reassortants are composed of the bovine rotavirus strain WC3 (Wistar Calf 3) genome background. Four of the reassortants express one of the human outer capsid glycoproteins (VP7s) of G1, G2, G3, and G4 serotype specificity each, along with the bovine spike protein (VP4) from the P7[5] WC3 strain. The fifth reassortant contains the human spike protein of P1A[8] serotype specificity, while retaining the bovine outer capsid glycoprotein of the G6 WC3 strain.

- **Manufacture, process controls and characterization:**

Manufacrurer:

- All RotaTeq™ drug substance manufacturing operations, from raw materials through frozen redispensed bulk, are performed at the following site:

Merck Sharp & Dohme Corp.Sumneytown Pike,P.O. Box 4, West Point, Pennsylvania, U.S.

- **Control of Materials**

- All raw materials used in the production of rotavirus vaccine are controlled and tested to ensure that quality acceptance criteria are met.
- The materials used in the production of rotavirus vaccine are in compliance with the requirements set forth in the *Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products* (EMEA/410/01), as well as the U.S. Food and Drug Administration (U.S. FDA).
- Information regarding the used strain & cell substrate is mentioned in detail in the MA file.

- **Control of Materials**

-List of raw materials of Pharmacopoeial and In-House Standard with relevant COAs are provided.
-Information regarding the used strain & cell substrate is mentioned in detail in the MA file.

- **Controls of Critical Steps and Intermediates**

- Process parameter and the Critical quality attribute for the manufacturing process stages had been identified.
- Information on the quality control of the intermediate had been submitted with description of the acceptance criteria of tests and process parameter.

- **Process Validation**

-The DS manufacturing process has been validated adequately. All process parameters were maintained and all CQA were achieved.
- Tests results of critical quality attribute and results for critical parameter attribute in each stage of DS manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency.

- **Control of Drug substance:**
- **Specification**

- Drug Substance Release Tests and Specifications are provided in the MA file

- **Analytical Procedures.**

- All analytical procedures either pharmacopeia or in house developed were described. The analytical procedures that need validation are clearly mentioned and well described.

- **Reference Standards or Materials.**

-All reference standards used during manufacturing are well described in the MA file

- **Container closure system**

- Container closure validation was conducted on the containers used for holding and transporting vaccine bulk after a sterile-filtration step. The container may be a 5-L, 10-L, or 20-L stainless steel container with a 2-inch ladish fitting and corresponding gasket.

- **Stability of drug substance**

- Stability studies are being conducted to support the manufacturing strategy for this product, which includes three vaccine bulk intermediates: harvested virus fluids (HVF), filtered virus fluids (FVF), and redispensed virus fluids (RVF). These intermediates are to be stored at –80 to –60 °C for 5, 10, and 5 years, respectively. Progress to date in supporting this strategy is provided in MA file.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

- RotaTeq™ is filled into single-dose oral dosing tubes (ODTs). Each vaccine lot is prepared by aseptically combining aliquots of the five reassortant bulk viruses into sterile formulation buffer, which consists of stabilizer1 solution and Rotavirus Diluent.
-The virus concentrations in the final formulated bulk are controlled to ensure that the amount

of virus in the final filled container meets potency specifications at the time of release.

- Rotateq physical appearance is pale yellow to a pale yellow with a pink tint, clear liquid.

➢ **Pharmaceutical Development**

➢ **Formulation Development**

- Several formulations were used during the development of RotaTeq™. These formulations are assigned numbers, typically an R and a three-digit number. The compositions of the different formulations and their associated clinical protocols are Provided in MA file.

➢ **Overages**

- The release specifications for average deliverable volume on each lot of vaccine are >1.90mL and < 2.40 mL, ensuring that the release specifications on average deliverable volume are satisfied.

➢ **Physicochemical and Biological Properties**

- The following physical characteristics measured for RotaTeq™ are density, viscosity, acid neutralizing capacity, and freezing point depression. Acid neutralizing capacity and freezing point depression were mentioned in MA file.

➢ **Manufacturing Process Development**

- Manufacturing Process Development and information for the clinical lots is provided in MA file.

➢ **Container Closure System**

-The vaccine is supplied in injection-molded, low-density polyethylene (LDPE), oral dosing tubes with a twist-off cap.

-Container Clouser specifications are provided in MA file.

➢ **Microbiological Attributes**

- RotaTeq™ is provided in a single-dose oral dosing tube with no preservative.

Stringent procedures are followed to ensure the absence of microbial contamination in the final product intended for oral use.

➢ **Compatibility**

- Compatibility of the container and closure system with the product is determined by long term stability studies designed to test the product over the length of the proposed shelf life.

-Testing of container and closure integrity is included as part of these studies.

➢ **Manufacture of the drug product:**

Description of manufacturing process and process controls along with manufacturers and responsibilities.

➢ **Manufacturer**:

- All drug product manufacturing operations and Packaging operations are performed at the following site: Merck Sharp & Dohme Corp., Sumneytown Pike,P.O. Box 4, West Point, Pennsylvania, U.S.

➢ **Description of Manufacturing Process and Process Controls**

- The starting materials for RotaTeq™ are stabilizer solution, Rotavirus Diluent, and five

rotavirus reassortants in the form of frozen, sterile, redispensed virus fluids (RVF).
- The potency of each RVF used for formulation varies from batch to batch. A process flow diagram of the formulation, filling, inspection, and packaging processes is provided in MA file.

- **Control of critical steps and intermediates**

- Critical process parameters (CPPs), critical quality attributes (CQAs), and quality control testing for product release is indicated in the diagram at the appropriate process points.
-The critical steps of the DP manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- **Process validation and / or evaluation**

-The consistency of product manufacture for formulation and filling was demonstrated by process validation using a series of three lots, which are provided in MA file.
- Critical process parameters (CPPs) were determined, and critical quality attributes (CQAs) were measured. A process description and a process diagram are provided in MA file.

- **Product specification:**

- The tests that are performed for release of drug product during routine manufacture are listed in MA file. Stability specifications are also included in MA file specification sheet. This panel of tests are performed on the drug product to ensure safety, to confirm the identity, to quantify the potency, and to provide a measure of process consistency.
- The analytical procedures that will be used to release the drug product during routine manufacturing along with their validation are described in this MA file.
- Q-PCR Quantitation of Vero Cell DNA is used to quantify the amount of Vero cell DNA in rotavirus filtered virus fluids (FVF) bulks. The specification that has been assigned as the maximum amount of residual Vero cell DNA allowed per final filled container (FFC) is discussed in MA file.
- The excipients used in the stabilizer solution are listed along with their specifications and COA. There is no novel excipients used in RotaTeq™.

- **Reference Standards or Materials.**

- Information on characterization of Reference Material Used in analytical methods was provided in MA file.

- **Container closure system.**

- The vaccine is supplied in injection-molded, low-density polyethylene (LDPE), oral dosing tubes (ODTs) with a twist-off cap. Filled ODTs are referred to as final filled containers (FFCs).
- Sample diagrams illustrating the FFC are provided in MA file.
- Identity of materials of construction together with their specifications are described.

- **Stability of the drug product.**

- Based on available stability data,

Approved shelf life for the Finished product: 24 months when stored at 2-8°C
Approved Storage Conditions:
- Store at temperature 2-8ºC
- Rota Should be administrated as soon as possible after being removed from refrigerator.

- protect from Light.

3. Non –clinical aspect:

- RotaTeq is an oral vaccine containing 5 live human-bovine reassortant strains (G1, G2, G3, G4, and P1), which is indicated for the prevention of rotavirus gastroenteritis in infants and children. RotaTeq is administered orally in a 3-dose regimen beginning at the age of 6 to 12 weeks with 1- to 2-month intervals between doses.

➢ **Pharmacology:**

- Traditional pharmacodynamic studies in animal models have not been performed for RotaTeq™ because the viruses in this live viral vaccine do not replicate in any relevant animal model. Since there is an obligate requirement for the virus to replicate in order to induce immunity, direct pharmacodynamic assessment of the vaccine in animal models is not meaningful.
- Although the EMA "Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines" (CPMP/SWP/465/95) and the "WHO Guidelines on Nonclinical Evaluation of Vaccines" recommend that immunogenicity studies in animal models be conducted. However, clinical trials for Rotateq began in 1993, 5 to 10 years before the establishment of the EMA and WHO guidances, respectively. Thus, by the time the EMA guidance was implemented in 1998, a significant body of clinical data on the pharmacodynamics (immunogenicity and efficacy) of the vaccine in over 1,500 infants was collected. Therefore, no nonclinical pharmacology studies were performed for RotaTeq.

➢ **Pharmacokinetics:**

- Traditional pharmacokinetic studies have not been performed for RotaTeq. According to the EMA "Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines" (CPMP/SWP/465/95), pharmacokinetic studies of vaccines are not normally needed.

➢ **Toxicology:**

- Nonclinical studies supporting the safety of this vaccine include a 10-week subacute oral toxicity study in mice, and 6 Vero cell DNA uptake studies in rats. The mouse toxicity study provides an extensive evaluation of the nonclinical safety of RotaTeq. In this study, the vaccine was well tolerated and there were no treatment-related antemortem or postmortem findings. The Vero cell DNA uptake studies were performed to support the levels of residual Vero cell DNA in RotaTeq. These uptake studies demonstrated that the levels of residual Vero cell DNA in RotaTeq are acceptable. RotaTeq, however, was not evaluated in reproductive toxicity studies as this is a pediatric vaccine and is not indicated for use in adults. The genetic toxicity and the oncogenic potential of RotaTeq were also not evaluated, as according to the EMA and WHO guidances, these types of studies are not required for vaccines. Similarly, local tolerance studies were also not conducted since RotaTeq is indicated for oral use and thus there is very little likelihood of skin or ocular irritation in vaccine recipients.

4. **Clinical aspect:**

➢ **Clinical Overview**

- Merck decided to continue development of Rotavirus vaccine (Rotavirus Vaccine, Live, Oral, Pentavalent), using the most prevalent human rotavirus serotypes are G1, G3, and G4 in conjunction with P1A, and G2 in conjunction with P1B, for which Merck conducted 8 Studies divided into Phase I/II studies (5 studies) and Phase III (3 studes). A Phase I/II clinical trial was conducted by Merck to select the formulation, potency (dose), and reassortant composition of RotaTeq™. A Phase III clinical trial was conducted by Merck to assess the efficacy, immunogenicity, and safety.

Overview of Key Clinical Studies

➢ **Clinical Efficacy:**

- Among healthy infants aged 6 to 12 weeks at enrollment who received RotaTeq™ or placebo, the clinical development program demonstrated the following:
- RotaTeq™ is efficacious in preventing rotavirus gastroenteritis (RVGE) of any severity caused by the vaccine-included serotypes (G1, G2, G3, and G4) during the first rotavirus season following vaccination, with sustained efficacy observed through the second season post-vaccination.
- Vaccination significantly reduces healthcare utilization associated with RVGE, including hospitalizations and emergency department visits, compared to placebo.
- Based on limited data, protective efficacy extends to RVGE caused by the G9 serotype during the first rotavirus season post-vaccination.
- The vaccine maintains efficacy regardless of the dosing schedule evaluated.
- RotaTeq™ can be administered concomitantly with routinely recommended pediatric vaccines, including hexavalent vaccines, without compromising efficacy.
- In premature infants (gestational age ≤36 weeks), the vaccine demonstrates efficacy against RVGE of any severity.
- The vaccine retains efficacy at expiry potency.
- Phase II data suggest that the P1 reassortant component contributes independently to overall vaccine efficacy.

➢ **Clinical Immunogenicity analysis**

In the same population:

- RotaTeq™ demonstrates an overall immunogenic profile.
- Concomitant administration with other licensed pediatric vaccines does not adversely affect immunogenicity.
- Consistency across manufacturing lots was confirmed, with three evaluated lots inducing comparable antibody responses, as measured by serum neutralizing antibody (SNA) geometric

mean titers (GMTs) against rotavirus serotypes (G1, G2, G3, G4, and P1), as well as serum anti-rotavirus IgA responses.

➢ **Clinical Safety**

The safety profile of RotaTeq™ was evaluated in healthy infants aged 6 to 12 weeks at enrollment:

- The vaccine is generally well tolerated.
- No increased risk of intussusception was observed within 42 days following vaccination compared to placebo.
- Furthermore, no evidence of increased risk was identified within 7-, 14-, 60-, or 365-days following vaccination.
- Adverse events of special interest (including diarrhea, fever, irritability, vomiting, and hematochezia) were generally comparable between groups; however, a slight increase in mild diarrhea and vomiting was observed among vaccine recipients.
- The vaccine is well tolerated when administered concomitantly with other pediatric vaccines, including hexavalent formulations.
- A favorable safety profile was also observed in premature infants (gestational age ≤36 weeks).
- Vaccine virus shedding was infrequent and occurred predominantly within the first week following the initial dose, indicating a low potential risk of fecal-oral transmission.

➢ **Benefit-Risk Analysis**

- Rotavirus infection represents a significant global public health burden, affecting nearly all children by the age of five years, irrespective of socioeconomic or environmental conditions. It is associated with substantial morbidity and mortality, including millions of clinic visits and hospitalizations annually, and hundreds of thousands of deaths worldwide. Evidence from active surveillance studies indicates that rotavirus may account for up to 40-60% of diarrhea-related hospitalizations in children under five years of age.
- Currently, management of RVGE is primarily supportive. Although rotavirus vaccines are available, access remains limited in some settings. The Phase III clinical program for RotaTeq™, including the large-scale REST study, demonstrated high efficacy, with approximately 98% protection against severe RVGE caused by the most prevalent serotypes (G1-G4). In addition, the vaccine significantly reduced hospitalizations (by 95.8%) and emergency department visits (by 93.4%) related to RVGE compared to placebo.
- The safety profile is favorable, with no increased risk of intussusception observed and only a slight increase in mild, transient gastrointestinal adverse events. These findings are supported by extensive pre-licensure safety and efficacy data derived from well-designed and robust clinical trials.

Overall, the demonstrated clinical benefits of RotaTeq™, particularly in preventing severe disease and reducing healthcare burden, clearly outweigh the minimal risks associated with vaccination. Given the universal susceptibility to rotavirus infection and the absence of specific risk factors for severe disease, RotaTeq™ represents an important intervention in pediatric public health.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.