Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Rotarix, Human rotavirus, live attenuated (Rotavirus vaccine, live)

RMP version to be assessed as part of this application	
RMP Version number	24.0
Data lock point for this RMP	31 December 2023
Date of final sign off	27 June 2024

Rationale for submitting an updated RMP
1. The company proposes to remove the long-term genetic stability, classified as missing information, from the list of safety concerns, in line with the review of the available data and in accordance with GVP V revision 2 criteria. 2. The company proposes to remove information related to the lyophilized formulation of Rotarix: in line with the introduction of the liquid PCV-free presentation, the Company decided to discontinue the production of the lyophilized formulation. A type 1B variation to discontinue the lyophilized presentation was submitted to EMA in April 2024, CHMP favorable opinion was received in May 2024 (EMA/CHMP/236142/2024). 3. Minor editorial changes are introduced.

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in EU-RMP version 24**
Part 1		Updated to reflect current approved product information and lyophilized formulation removed from pharmaceutical forms.
Part II	MODULE SI	Updated based on latest literature and information from 2022 EuroRotaNet Annual report.
	MODULE SII	Minor updates
	MODULE SIII	Clinical trial exposure data have been updated as per DLP.
	MODULE SIV.1	Minor updates
	MODULE SIV.2	Updated data as per the DLP
	MODULE SV.1.2	Removal of the exposure data by country and formulation (Table SV.1) according to the new EMA guidance “Anonymization of Protected Personal Data and assessment of 08 April 2024. Commercially Confidential Information during the preparation of RMPs (main body and annexes 4

		and 6)". Addition of the cumulative exposure data.
	MODULE SVII	Removal of missing information from the list of safety concerns
Part III	III.I	Removal of specific adverse reaction follow-up questionnaire for Rotavirus Vaccine & Vaccination Failure/Lack of Efficacy and other forms of routine PV activities as a consequence of the removal of long term genetic stability of the vaccine virus strain from the missing information
	III.2	Removal of additional PV activity of ARSP, as a consequence of removal of missing information.
Part V	V	Update of risk minimization measures to reflect the removal of long term genetic stability of the vaccine virus strain from the missing information
Part VI		Minor updates Removal of long term genetic stability of the vaccine virus strain missing information. (II.A and II.B)
Part VII	Annex 4	Removal of specific adverse reaction follow-up questionnaire from the RMP pertaining to Rotavirus Vaccine & Vaccination Failure/Lack of Efficacy as a consequence of the removal of long term genetic stability of the vaccine virus strain from the missing information
	Annex 7	Update of references
	Annex 8	Aligned and updated according to current RMP version 24.0.

Other RMP versions under evaluation		
RMP Version number	**Submitted on**	**Procedure number**
Not applicable	Not applicable	Not applicable

Details of the currently approved RMP		
Version number	**Approved with procedure**	**Date of approval (opinion date)**
23	EMEA/H/C/000639/II/0125	10 June 2022

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

ABBREVIATIONS

ADR	Adverse Drug Reaction
AGE	Acute gastroenteritis
AE	Adverse Event
aRMM	additional Risk minimization measures
ARSP	Australian Rotavirus Surveillance
CEP	Clinical and epidemiology development plan
CI	Confidence Interval
DLP	Data Lock Point
DSUR	Development Safety Update Report
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EuroRotaNet	European Rotavirus Network
GE	Gastroenteritis
HCP	Health Care Professionals
HIV	Human Immunodeficiency Virus
HRV	Human Rotavirus
IMSS	Mexican Institute of Social Security (Instituto Mexicano del Seguro Social)
IPV	Inactivated Poliovirus Vaccine
IQR	Inter Quartile Range
IRR	Incidence rate ratio
IS	Intussusception
KD	Kawasaki's disease
LRTI	Lower respiratory tract infection
MAH	Market Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIP	National Immunisation Programmes
PASS	Post-Authorisation Safety Study
PAM	Post-Authorisation Measure
PBRER	Periodic Benefit Risk Evaluation Report
PCV	Porcine Circovirus
PhV	Pharmacovigilance
PL	Package Leaflet
PMS	Post Marketing Surveillance
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
RCWG	Rotavirus Classification Working Group
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
RV	Rotavirus
RVGE	Rotavirus Gastroenteritis
SCID	Severe Combined Immunodeficiency Disorder
SGE	Severe Gastroenteritis

SmPC	Summary of Product Characteristics
UI	Uncertainty Interval

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Rotarix

Trademarks not owned by the GlaxoSmithKline group of companies
RotaShield
Rotateq

TABLE OF CONTENTS

PAGE

LIST OF ANNEXES

PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Human rotavirus, live attenuated (Rotavirus vaccine, live)
Pharmacotherapeutic group(s) (ATC Code)	Rotavirus diarrhoea vaccines (J07BH01)
Marketing Authorization Holder/ Applicant	GlaxoSmithKline Biologicals S.A.
Medicinal products to which this RMP refers	Rotavirus vaccine, live, attenuated
Invented name(s) in the European Economic Area (EEA)	*Rotarix*
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Viral vaccine
	Summary of mode of action: The immunologic mechanism by which *Rotarix* protects against rotavirus gastroenteritis is not completely understood. While a formal correlate of protection has not been established, association between serum IgA seropositivity and protection against severe RVGE has been shown (Cheuvart, 2014)
	Important information about its composition: Live attenuated human rotavirus RIX4414 strain.
Reference to the Product Information	Please refer to the approved product information
Indication(s) in the EEA	Current (if applicable): *Rotarix* is indicated for the active immunization of infants aged 6 to 24 weeks for prevention of gastroenteritis due to rotavirus infection. The use of *Rotarix* should be based on official recommendation.
Dosage in the EEA	Current (if applicable): The vaccination course consists of two doses. The first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should preferably be given before 16 weeks of age but must be completed by the age of 24 weeks. *Rotarix* may be given with the same posology to preterm infants born after at least 27 weeks of gestational age.

Pharmaceutical form(s) and strengths	Current (if applicable): *Rotarix* oral suspension in pre-filled oral applicator *Rotarix* oral suspension in squeezable tube Strength: Human rotavirus RIX4414 strain (live, attenuated) at not less than $10^{6.0}$ $CCID_{50}$/dose
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Prevention of gastroenteritis

Rotarix is indicated for the active immunization of infants aged 6 to 24 weeks for prevention of gastroenteritis due to rotavirus infection. The use of Rotarix should be based on official recommendation.

Incidence

Before the introduction of rotavirus (RV) vaccination, RV was the most common cause of severe acute gastroenteritis (AGE) in infants and children worldwide (Parashar, 2003; Cunliffe, 1998 and Kane, 2004). RV infection was universal and affected almost all children by the age of 5 years (Velazquez, 1996) with a peak incidence between 6 and 24 months of age (Meloni, 2011). After the introduction of RV vaccination, substantial reduction in morbidity and mortality due to RV has been observed, but gastroenteritis (GE) remains a major cause of childhood death in developing countries.

In 2016, the worldwide incidence of RV infection in children <5 years of age was estimated at 0.42 (95% uncertainty interval [UI] 0.30 – 0.53) cases per child-year and the incidence of severe diarrhoea due to RV was estimated to be 29.4 per 1,000 child-years (95% UI 22.2 – 38.0) (Troeger, 2018). In Western Europe, the estimated incidence of RV cases was 219.2 per 1,000 children (95% UI 143.9-327.8) and in Central Europe 722.6 per 1,000 children (95% UI 501.7-1,027.8) with variation between countries, ranging from 78.0 (95%UI 52.8-115.5) to 860.8 (95% UI 585.8-1268.7) per 1,000 children in Spain and in Poland, respectively (Troeger 2018).

Following the introduction in the National immunization program (NIP) in Belgium, England/Wales and Germany, the pooled incidence rate ratio (IRR) of 2 years post vaccine implementation was 0.58 (95% confidence interval [CI] 0.44-0.77) corresponding to a 42% (95% CI 23-56%) overall reduction in RV incidence (Verberk, 2021). In United Kingdom (UK), the laboratory-confirmed RV infection in infants < 1 year decreased by 77 – 88% in each of the 5 years following RV vaccine implementation (Gower, 2021).

Death rate due to RV is not easily quantifiable in developed countries. In Western Europe, RV-specific mortality rate is estimated at 0.2 per 100,000 children <5 years, leading to an estimate 50 deaths in 2016 (95% UI 38 – 64) (Troeger, 2018).

Prevalence

In 2016, 258 million episodes of diarrhea were attributed to RV infection in children <5 years of age, with an estimated 18,882,800 severe cases and 1,537,000 hospitalizations (Troeger 2018).

Prevalence of RV GE is usually higher in children aged from 6 to 24 months. A multicenter prospective study conducted in children <3 years of age in Spain showed that more than 70% of RV GE cases were reported among children aged 6 to 24 months with 42.8% reported in the age 12 to 24 months (Aristegui, 2016).

Evidence of indirect effect of the vaccine and herd immunity is also observed on all-cause AGE and in age categories not directly targeted by the vaccine indication. In a meta-analysis covering 49 countries worldwide, Burnett et al. found a median reduction of 36% (IQR, 23 – 47) among children < 5 years of age in AGE hospitalization compared to before RV vaccine introduction (Burnett 2020).

In UK, in the 5 years following vaccine introduction, there was a large reduction in laboratory-confirmed RV infections in the >65-year-olds (Gower 2021).

Rotavirus genotypes

RVs are classified as a genus within the family Reoviridae. They contain a triple-layered capsid encasing 11 genome segments of double stranded RNA. The RV genome encodes six structural proteins (VP1 to VP4, VP6 and VP7) and five to six non-structural proteins (NSP1 to NSP5/NSP6).

The International committee on taxonomy of viruses has recognized at least nine species of RV (RV A to Rotavirus J) defined on the basis of immune reactions to the VP6 protein. Group A RV (RVA) are the most common cause of GE in humans.

There are more than 200 genotypes encompassing all 11 RVA genome segments but the binary classification system based on genetic and antigenic structure of the two structural proteins VP7 and VP4 is still globally used and determine respectively the G and P genotypes (RCWG, 2015). The RCWG extended and developed this classification to a nucleotide sequence-based classification system for the complete genome of RVA strains; in this system, human RVA strains are classified as Wa-like, DS-1-like or AU-1-like (Matthijnssens, 2008). The most prevalent RVA genotypes identified worldwide affecting humans are G types 1 to 4, G9 and G12 and P types P[4], P[6] and P[8] (Matthijnssens, 2012). Predominant genotypes such as G1P[8], G3P[8] or G12P[8] have a Wa-like constellation, while G2P[4] genotype usually possess a DS-1-like constellation (Jere, 2011).

The extensive diversity in the genome of RV strains may influence the epidemiology of RV disease via several mechanisms such as reassortment of genes or sequential point mutations in genes.

In Europe, the EuroRotaNet network is gathering comprehensive information on the co-circulating RV strains. Before RV vaccine introduction, G1P[8] was the most prevalent strain in the majority of European countries (EuroRotaNet Annual Report 2022). Further to RV vaccine introduction, concurrently to a decrease in overall incidence of RVGE, changes in the prevalence of co-circulating genotypes were noticed (EuroRotaNet Annual Report 2022):

- G1P[8] decreased from 62% in 2007-2008 to 31% in 2014-2015 of single type strains . It reached a minimum of 8% in 2016-2017 to remain stable around 10% of the strains typed for the subsequent years. In 2020-2021, the proportion of G1P[8] strains detected increased, mainly through detections in two countries, Greece and Italy while in the other EuroRotaNet countries it remained low. This needs to be interpreted in the context of national increases in rotavirus vaccine uptake. As seen in Germany and the UK these G1P[8] could either wild-type or vaccine derived. Currently, Greece and Italy are not able to distinguish wild-type G1P[8] strains from vaccine derived strains either through sequencing or using a validated qRT-PCR assay test G1P[8].
- Since 2015-2016, annual fluctuation in dominant RV genotypes is observed: G9P[8] in 2015-2016, G2P[4] in 2016-2017 and G3P[8] from 2017-2018 to 2019-2020, then G9P[8] back in 2020-2021 and G3P[8] in 2021-2022.

Natural fluctuation of co-circulating strains is also noticed in European countries without RV vaccination programme. In France or in Denmark, over the recent years G9P[8] was found to be the most predominant genotype succeeding to G1P[8] (Kaplon, 2017, EuroRotaNet annual report 2022).

SI.1.1 Demographics of the population in the authorized indication

Rotarix is intended for the general pediatric population from the age of 6 weeks; vaccination must be completed by 24 weeks of age. Rotarix does not target a specific population who could receive frequent, concomitant specific treatments. It is however expected that the subjects may receive concomitant vaccinations.

SI.1.2 The main existing treatment options

No specific treatment/standard of care exists for rotavirus infection. Good hygiene like handwashing and cleanliness are important but are not enough to control the spread of the disease. To date, vaccination is the only effective measure to reduce the burden of RV disease.

SI.1.3 Natural history of the indicated condition in the untreated population, including mortality and morbidity

RV is transmitted by the fecal-oral route and is highly contagious when transmitted within the same species. Viral replication within the intestinal tract can result in shedding of ≥ 1010 infectious particle (PFU)/ml of feces (Bishop, 1996).

RV is the leading cause of infantile GE and can occur repeatedly in humans of all ages. Most infections are asymptomatic or associated with mild enteric symptoms. Complications such as severe dehydration with parenteral administration of fluids and life-threatening diarrhea may happen in more susceptible younger age groups. The disease lasts on average 3 to 8 days.

In temperate climate, RV seasonal peak usually occurred from autumn to spring. After RV vaccine implementation, a smooth distribution of RV infections was observed across seasons (Sabbe, 2016; Mukhopadhya, 2017).

SI.1.4 Important co-morbidities

Rotarix is intended for the general pediatric population. The administration of the vaccine is currently recommended for infants of the age of 6 weeks to 24 weeks. There are no common co-morbidities found for this population.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Rotarix is a mature product with more than 19 years of post-marketing clinical exposure. There are no outstanding non-clinical safety concerns. The pharmacological, and toxicological effects of Rotarix have been well characterized in animals, and no new non-clinical information has come to light that would affect the safety of Rotarix for clinical use.

There are no non-clinical findings which warrant inclusion in the list of safety concerns.

Key safety findings from non-clinical studies and relevance to human usage:

Table 2 Key safety findings from non-clinical studies

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity including: Repeat-dose toxicity: no key safety findings	N/A

The young Fischer F344 rat has been used as an appropriate susceptible animal model to study the toxicity of Rotarix.

Rotarix is non-toxic when tested in the young Fischer F344 rat. The vaccine is well tolerated, does not induce clinical signs, any clinical disease symptom, hyperthermia or signs of inflammation in the gastrointestinal tract or adjacent lymph nodes. The final vaccine formulation does not contain any new or hazardous excipient and is therefore considered devoid of any toxicity.

The non-clinical safety results indicated that Rotarix was well tolerated without key safety findings.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Rotarix was first approved on July 12th, 2004. Accounting for an extensive post-marketing history, a brief summary of clinical trial experience is presented below.

The cumulative number of subjects that have received Rotarix in GSK-sponsored interventional trials part of the Rotarix clinical development plan (CDP) is 67 316 [55 923 received the lyophilized formulation; 6999 received the liquid formulation and 4394 out of specification (lower potency formulation of Rotarix that was not part of the marketing authorization (MA))]. In studies using Rotarix in other GSK CDPs, of 9959 subjects, the overall number of subjects who have received Rotarix is 9812 (all have received the lyophilized formulation) and 147 subjects have not received Rotarix.

Table 3 Exposure (by age group, gender and racial origin)

		Rotavirus vaccine lyo in CEP N = 55923		Rotavirus vaccine liq in CEP N = 6999		Rotavirus vaccine out of spec in CEP N = 4394		Rotavirus vaccine pooled in CEP N = 67316		Placebo in CEP N = 47449		Total N = 114765	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at vaccination	Mean	9.4	-	16.3	-	11.9	-	10.3	-	10.3	-	10.3	-
	SD	37.8	-	107.9	-	19.5	-	49.3	-	49.5	-	49.4	-
	Median	8.0	-	9.0	-	9.0	-	8.0	-	8.0	-	8.0	-
	Minimum	1.0	-	5.0	-	5.0	-	1.0	-	2.0	-	1.0	-
	Maximum	2347.0	-	2343.0	-	202.0	-	2347.0	-	2325.0	-	2347.0	-
	Missing	0	-	0	-	3	-	3	-	0	-	3	-
Age at vaccination	0-11M	55850	99.9	6900	98.6	4320	98.3	67070	99.6	47350	99.8	114420	99.7
	1-6Y	51	0.1	73	1.0	71	1.6	195	0.3	64	0.1	259	0.2
	7-17Y	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	18Y-	22	0.0	26	0.4	0	0.0	48	0.1	35	0.1	83	0.1
	Unknown/Missing$	0	0.0	0	0.0	3	0.1	3	0.0	0	0.0	3	0.0
Gender	Female	27470	49.1	3406	48.7	2158	49.1	33034	49.1	23226	48.9	56260	49.0
	Male	28453	50.9	3593	51.3	2236	50.9	34282	50.9	24223	51.1	58505	51.0
Race	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Black	4313	7.7	135	1.9	321	7.3	4769	7.1	2284	4.8	7053	6.1
	White	817	1.5	807	11.5	295	6.7	1919	2.9	52	0.1	1971	1.7
	White-Caucasian	10054	18.0	1773	25.3	897	20.4	12724	18.9	6560	13.8	19284	16.8
	White-Arabic/North African	35	0.1	13	0.2	0	0.0	48	0.1	17	0.0	65	0.1
	Oriental	606	1.1	0	0.0	1082	24.6	1688	2.5	613	1.3	2301	2.0
	Oriental-East/South East Asian	1822	3.3	834	11.9	273	6.2	2929	4.4	1490	3.1	4419	3.9
	Oriental-Central/South Asian	677	1.2	8	0.1	355	8.1	1040	1.5	638	1.3	1678	1.5
	Oriental-Japanese	548	1.0	413	5.9	0	0.0	961	1.4	261	0.6	1222	1.1

		Rotavirus vaccine lyo in CEP N = 55923		Rotavirus vaccine liq in CEP N = 6999		Rotavirus vaccine out of spec in CEP N = 4394		Rotavirus vaccine pooled in CEP N = 67316		Placebo in CEP N = 47449		Total N = 114765	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
	Oriental-Chinese	4089	7.3	1666	23.8	6	0.1	5761	8.6	5765	12.1	11526	10.0
	Hispanic	28444	50.9	1	0.0	296	6.7	28741	42.7	26803	56.5	55544	48.4
	Asian	549	1.0	546	7.8	0	0.0	1095	1.6	0	0.0	1095	1.0
	Native Hawaiian Or Other Pacific Islander	4	0.0	2	0.0	0	0.0	6	0.0	0	0.0	6	0.0
	American Indian Or Alaska Native	8	0.0	10	0.1	0	0.0	18	0.0	0	0.0	18	0.0
	Other	3957	7.1	791	11.3	869	19.8	5617	8.3	2966	6.3	8583	7.5

n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
$Study Rota-014 for these subjects no information about the activity date to calculate their age
Data from completed trials as of 11 Jul 2023The group HRV pooled provides the total exposure to *Rotarix* (includes lyo/liq or out of specification)

HRV out of spec - The Human Rotavirus (HRV) vaccine formulation used in some of the early clinical development studies was not the same as the current marketed formulation. Hence, the groups receiving HRV from these studies are collected in one group called the 'out of specification group'.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Rotarix has been extensively studied in clinical studies and has a well-defined safety profile that is supported by over 19 years of post-marketing safety information.

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
History of allergic disease or reactions likely to be exacerbated by any component of the vaccine(s)	To avoid hypersensitivity reactions to the active substance or to any of the excipients.	NO	Hypersensitivity to the active substance or to any of the excipients. (Contraindication in EU SmPC).
History of intussusception	Following the experience of the first RV vaccine, an oral tetravalent (G1-4) rhesus-human reassortant vaccine (Rotashield) for which post-marketing surveillance indicated a higher-than-expected rate of intussusception.	NO	History of intussusception (contraindication in EU SmPC). As a precaution, healthcare professionals should follow-up on any symptoms indicative of intussusception (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever) since data from observational safety studies indicate an increased risk of intussusception, mostly within 7 days after rotavirus vaccination. Parents/guardians should be advised to promptly report such symptoms to their healthcare provider. (Special warnings and precautions for use in EU SmPC)
Uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception.	Following the experience of the first RV vaccine, an oral tetravalent (G1-4) rhesus-human reassortant vaccine (Rotashield) for which, post-marketing surveillance indicated a	NO	Subjects with uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception (contraindication in EU SmPC). There are no data on the safety and efficacy of

	higher-than-expected rate of intussusception.		Rotarix in infants with gastrointestinal illnesses or growth retardation. Administration of Rotarix may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk. (Special warnings and precautions in EU SmPC)
Family history of congenital or hereditary immunodeficiency	It is a live attenuated vaccine.	NO	Severe Combined Immunodeficiency (SCID) disorder (contraindication in EU SmPC)
Infants who have known or suspected immunodeficiency	It is a live attenuated vaccine.	NO	Asymptomatic and mildly symptomatic HIV infections are not expected to affect the safety or efficacy of Rotarix. A clinical study in a limited number of asymptomatic or mildly symptomatic HIV positive infants showed no apparent safety problems. Administration of Rotarix to infants who have known or suspected immunodeficiency, including in utero exposure to an immunosuppressive treatment, should be based on careful consideration of potential benefits and risks. (Special warnings and precautions in EU SmPC)
Children born prematurely	As a precaution for safety concerns, it was not studied in this population.	NO	Rotarix may be given with the same posology to preterm infants born after at least 27 weeks of gestational age. (Posology in EU SmPC)
Administration of long-acting immune-modifying drugs	It is a live attenuated vaccine	NO	Rotarix should be administered with caution to individuals with immunodeficient close contacts, such as individuals with malignancies, or who are otherwise immunocompromised or individuals receiving

			immunosuppressive therapy (Special warnings and precautions for use in EU SmPC)
Acute disease and/or fever	To avoid possible cumulative effect of the vaccine's reactogenicity with ongoing disease and symptoms. It would also bias the safety assessment of the vaccine.	NO	Administration of Rotarix should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication for immunization (contraindication in EU SmPC).
Acute Gastroenteritis	To avoid possible cumulative effect of the vaccine's reactogenicity with ongoing disease and symptoms. It would also bias the safety assessment of the vaccine.	NO	The administration of Rotarix should be postponed in subjects suffering from diarrhoea or vomiting (contraindication in EU SmPC).

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Ability to detect adverse reactions	**Limitation of trial program**	**Discussion of implications for target population**
Which are rare	Based on the most recent safety pooling with a DLP of 11 July 2023; 67 316 clinical trial subjects received Rotarix.	In the studies, only ADRs with a frequency greater than 1 in 22,438 could be detected.
Due to prolonged exposure	There is no prolonged exposure with prophylactic vaccines.	NA
Due to cumulative effects	There is no cumulative exposure nor specific organ toxicity that has been observed with Rotarix.	NA
Which have a long latency	There is no potential or identified risk that could have a long latency following vaccination with Rotarix.	NA

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table 4 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment	 Not included in the clinical development program Not included in the clinical development program
Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program Study Rota-022, was conducted in the frame of the Pharmacovigilance plan in immunocompromised children infected with HIV. Total vaccinated cohort was of 100 subjects (50 subjects vaccinated with HRV vaccine). The results from this study did not indicate a safety signal specific to these subpopulations. Not included in the clinical development program
Population with relevant different ethnic origin	Vaccine Efficacy trials have been conducted across multiple geographies and continents. VE was mostly correlated with the socio-economic status, not directly with ethnicity.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other: Children born prematurely	Study Rota-054, was conducted in the frame of the Pharmacovigilance plan in preterm infants; 1009 subjects (670 vaccinated with HRV vaccine) including 802 subjects with gestational period 31-36 weeks, 206 subjects with gestational period 27-30 weeks and 1 subject with gestational age < 27 weeks. The results from this study did not indicate a safety signal specific to these subpopulations (Omenaca, 2012)
Other: Twins	Study Rota-052 was conducted in the frame of the Pharmacovigilance plan to explore the horizontal transmission of the *Rotarix* vaccine strain between twins within a family, 100 pairs of twins (100 subjects in the HRV vaccine group and 100 subjects in the placebo group) received at least one dose of HRV/placebo.

	This study showed that the transmission of vaccine strains among twins was lower than 20% and likely lower in a general children population where the level of contact is less intense. The HRV vaccine strains transmitted to placebo children did not result in clinical gastroenteritis disease or in adverse events (AEs) (Luis, 2011)

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-authorization exposure

Changes to the cumulative post-marketing exposure do not alter considerations on the risk evaluation for Rotarix.

SV.1.1 Method used to calculate exposure

Information on the actual number of people exposed to Rotarix in the different countries is not available to the Marketing Authorization Holder due to limited availability and heterogeneity of data sources between and within countries (e.g., multiple national immunization schedules, specific mass vaccination campaign, incidence of the disease, catch-up, outbreak containment). Therefore, subject exposure is approximated by the number of doses distributed which is the most reliable data available regarding subject exposure for a vaccine in a post-marketing setting.

. It is important to note that the sales database from which data are retrieved is an in-house 'living' database and is subject to updates and corrections depending on information provided by GSK local country subsidiaries (e.g., vaccine doses may be returned by subsidiaries to the central warehouse). These constant updates may result in discrepancies between consecutive queries of the database.

SV.1.2 Exposure

Cumulative (since launch until DLP 31 December 2023) post-marketing exposure to Rotarix is estimated to be 908 384 135 doses. As vaccination with Rotarix could vary between 1 and 2 doses per subject in accordance with local recommendations and compliance with the vaccination schedule, cumulative post-marketing exposure to Rotarix is estimated as being between 454 192 068 and 908 384 135 doses.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

GSK is not aware of any potential for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Long term genetic stability of the vaccine virus strain (concern that genetic variations in the Rotarix vaccine strain could lead to clinical symptoms of gastroenteritis) classified as a missing information is proposed to be removed from the list of safety concerns.

Reasons for the proposed removal from the list of safety concerns:

- Rotarix is well established product and has been in market for over 19 years [post-marketing exposure since launch until 31 December 2023 (DLP of this RMP) is estimated as being between 454 192 068 and 908 384 135 doses]. The cumulative review of the reports received for vaccination failure and Rotavirus infection did not provide evidence of impaired vaccine effectiveness or an increased incidence of rotavirus infection. This is aligned with data reported in previous PBRERs.
- Regular and systematic review of the literature related to lack of efficacy and impact of strain diversity on *Rotarix* vaccine effectiveness did not show conclusive evidence that there is any consistent change in the pattern of circulating RV after introduction of RV vaccines, or a convincing difference in strain specific effectiveness. There is little evidence to suggest that drift or re-assortment events are increasingly causing GE symptoms in either unvaccinated contacts of RV vaccines, or in unvaccinated subjects who may encounter circulating vaccine strains.
- The results of EuroRotaNet study from 2006 until 2022 and the results of Australian Rotavirus Surveillance Program (ARSP) from June 1999 to December 2023, did not provide evidence that RV vaccination programs are driving the emergence of vaccine escape strains. The findings from both the studies support the hypothesis that the increase in proportion of RV strains is not linked to the use of RV vaccines.

  Considering the above which includes reports of Vaccination Failure and RV infection, data from the literature and results from the 2 two large surveillance studies, there is no evidence of genetic instability of the vaccine virus strain or that it represents a risk to the population, or that it is leading to impaired vaccine effectiveness or an increased incidence of rotavirus infection.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk: None

Important Potential Risk: None

SVII.3.2 Presentation of the missing information

There is no missing information associated with Rotarix.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 5: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None.
Important potential risks	None.
Missing information	None.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORIZATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are required:

Specific adverse reaction follow-up questionnaires:

Not applicable

Other forms of routine pharmacovigilance activities for long term genetic stability of the vaccine virus strain:

Not applicable

III.2 Additional pharmacovigilance activities

Not required

III.3 Summary Table of additional Pharmacovigilance activities

Table 6: Ongoing and planned additional pharmacovigilance activities

There are no ongoing and planned additional PV activities (Category 1-3 studies) for Rotarix.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

None

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Not applicable

V.2 Additional Risk Minimization Measures

There are no additional risk minimization measures for *Rotarix*.

V.3 Summary of risk minimization measures

Not applicable

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Rotarix (Rotavirus vaccine)

This is a summary of the risk management plan (RMP) for Rotarix. The RMP details important risks of Rotarix, how these risks can be minimized, and how more information will be obtained about Rotarix 's risks and uncertainties (missing information).

Rotarix 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rotarix should be used.

This summary of the RMP for Rotarix should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rotarix's RMP.

I. The medicine and what it is used for

Rotarix is authorized for the active immunization of infants aged 6 to 24 weeks for prevention of gastroenteritis due to rotavirus infection (see SmPC for the full indication). It contains human rotavirus, live attenuated as the active substance and it is given by oral administration. Further information about the evaluation of Rotarix's benefits can be found in Rotarix's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage Rotarix | European Medicines Agency (europa.eu).

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Rotarix, together with measures to minimize such risks and the proposed studies for learning more about Rotarix's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Rotarix are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rotarix. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None.
Important potential risks	None.
Missing information	None

II.B Summary of important risks

Not Applicable

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Rotarix.

II.C.2 Other studies in post-authorization development plan

There are no studies required for Rotarix.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

None