RotaTeq

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
N/0097	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/04/2024		PL	
IAIN/0095	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/11/2023	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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N/0094	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/03/2023	04/08/2023	Labelling	
IG/1524/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	15/08/2022	04/08/2023	Annex II	
IB/0092/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	24/06/2022	n/a		
T/0090	Transfer of Marketing Authorisation	14/03/2022	01/04/2022	SmPC, Labelling and PL	
N/0089	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/11/2021	01/04/2022	PL	

N/0088	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/07/2021	01/04/2022	PL	
PSUSA/2666/ 202011	Periodic Safety Update EU Single assessment - rotavirus vaccine pentavalent (live, oral)	08/07/2021	n/a		PRAC Recommendation - maintenance
II/0085	To update the RMP for RotaTeq to version 7.2 to meet the requirements and updated definitions in the Guideline on good pharmacovigilance practices (GVP) module V (EMA/838713/2011; Rev 2); consequently, the list of safety concerns is updated and a reclassification of important risks is proposed. In addition, the proposed RMP version 7.2 implements the removal of hypersensitivity and severe combined immunodeficiency (SCID) from the list of safety concerns as requested by the PRAC in PSUR procedure (PSUSA/00002666/201911). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	06/05/2021	n/a		
IA/0087/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	31/03/2021	n/a		

	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
PSUSA/2666/ 201911	Periodic Safety Update EU Single assessment - rotavirus vaccine pentavalent (live, oral)	25/06/2020	25/08/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2666/201911.
IB/0084/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	19/06/2020	n/a		
IA/0083/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	27/03/2020	n/a		

	Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
IB/0081	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/03/2020	25/08/2020	SmPC, Annex II, Labelling and PL	
N/0080	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/02/2020	25/08/2020	PL	
II/0079/G	This was an application for a group of variations. Replacement of the test method used for potency an identity testing of rotavirus-containing drug substance and drug product: Rotavirus- Multivalent Quantitative Polymerase Chain Reaction is being replaced by Second Generation Multivalent Quantitative Polymerase Chain Reaction Assay. In addition, the bulk identity testing will be moved from the Harvested Virus Fluids (HVF) intermediate to the Filtered Virus Fluids (FVF) intermediate to streamline the release testing process for bulk intermediates. The requested group of variations proposed no	14/11/2019	n/a		

	amendments to the Product Information. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol				
PSUSA/2666/201811	Periodic Safety Update EU Single assessment - rotavirus vaccine pentavalent (live, oral)	14/06/2019	n/a		PRAC Recommendation - maintenance
IG/0977	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	19/10/2018	n/a		
PSUSA/2666/201711	Periodic Safety Update EU Single assessment - rotavirus vaccine pentavalent (live, oral)	14/06/2018	n/a		PRAC Recommendation - maintenance
IB/0076	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/05/2018	26/04/2019	SmPC, Annex II, Labelling and PL	
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/09/2017	26/04/2019	Labelling	
IA/0073	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	22/09/2017	n/a		

PSUSA/2666/201611	Periodic Safety Update EU Single assessment - rotavirus vaccine pentavalent (live, oral)	22/06/2017	18/09/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2666/201611.
IB/0072	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	21/06/2017	n/a		
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/03/2017	18/09/2017	PL	
IB/0070	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	21/03/2017	n/a		
IG/0777	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2017	18/09/2017	SmPC, Labelling and PL	
IG/0758	A.1 - Administrative change - Change in the name and/or address of the MAH	11/01/2017	18/09/2017	SmPC, Labelling and PL	
N/0065	Update of the package leaflet with revised contact details of the local representatives. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2016	18/09/2017	PL	

PSUSA/2666/ 201511	Periodic Safety Update EU Single assessment - rotavirus vaccine pentavalent (live, oral)	09/06/2016	n/a		PRAC Recommendation - maintenance
II/0062	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	17/03/2016	n/a		
II/0061	Update of section 5.1 of the SmPC to reflect data on effectiveness against rotavirus acute gastroenteritis due to G12P[8] and effectiveness in children up to five years based on 3 post-authorisation studies. In addition, the MAH took the opportunity to bring the Annex II in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/12/2015	16/12/2016	SmPC and Annex II	With this procedure the MAH propose to update of section 5.1 of the SmPC to reflect data on effectiveness against rotavirus acute gastroenteritis due to G12P(8) and effectiveness in children up to five years based on 3 post-authorisation studies. In addition the MAH took the opportunity of this procedure to reformat the effectiveness data presentation in section 5.1 and update Annex II in compliance with the QRD template version 9.1.
II/0060	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	19/11/2015	n/a		
IG/0625	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/11/2015	n/a		
WS/0786	This was an application for a variation following a	17/09/2015	n/a		

	worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.z - Change in control of excipients in the Finished Product - Other variation				
PSUSA/2666/201411	Periodic Safety Update EU Single assessment - rotavirus vaccine pentavalent (live, oral)	11/06/2015	n/a		PRAC Recommendation - maintenance
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/06/2015	16/12/2016	PL	
IB/0057	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/03/2015	n/a		
PSUV/0050	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance
IG/0435	A.1 - Administrative change - Change in the name and/or address of the MAH	06/05/2014	19/02/2015	SmPC, Labelling and PL	
IG/0434	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	09/04/2014	n/a		
IB/0051	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/03/2014	19/02/2015	SmPC, Annex II, Labelling and PL	The CHMP requested the MAH in December 2013 to update the SmPC with a harmonised wording for rotavirus vaccines based on new epidemiological data that became available on intussusception. These data strengthen the existing evidence base that suggests a small increased risk of

					intussusception shortly after vaccination with Rotarix and Rotateq. A statement regarding any difference in risk between the two vaccines cannot, however, be made. Given that the vaccine attributable risk of intussusception remains small, the CHMP recommended that the balance of benefits and risks rotavirus vaccines remains favourable and requested the MAH that the SmPC should be updated to reflect that • Rotavirus vaccines carry an increased risk of intussusception, mostly within 7 days of vaccination. Up to 6 additional cases per 100,000 infants have been observed in the US and Australia against a background incidence of 33 to 101 per 100,000 infants (less than one year of age) per year, respectively. There is limited evidence of a smaller increased risk following the second dose. It remains unclear whether rotavirus vaccines affect the overall incidence of intussusception based on longer periods of follow up. • 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. The CHMP agreed that the wording proposed by the MAH submitted for this variation was in line with the CHMP request.

IB/0049	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	31/01/2014	n/a		
IB/0048	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	31/10/2013	n/a		
IB/0047/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	10/09/2013	n/a		
WS/0404/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of analytical methods in order to align with compendial procedures and guidances B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting	25/07/2013	n/a		

	material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/07/2013	29/01/2014	PL	
IG/0312	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/06/2013	n/a		
IB/0042	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	16/02/2013	29/01/2014	SmPC and PL	Irritability was included as an adverse event in section 4.8 of the SmPC in line with a request from CHMP following the assessment of PSURs 11 and 12. The PL was updated accordingly.
IG/0261/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	30/01/2013	n/a		
IB/0040	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time	21/11/2012	n/a		

	data				
II/0039	To add two adverse events (angioedema and anaphylactic reactions) to section 4.8 of the SmPC and section 4 of the PL based on post-authorisation spontaneous reporting data, and to update section 4.4 of the SmPC to include a warning in view of appropriate medical treatment to be in place in case of an anaphylactic event. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet for Cyprus and Malta. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	24/10/2012	SmPC, Annex II, Labelling and PL	The MAH has identified four cases of anaphylactic type reactions and a further 20 cases of angioedema/facial swelling. While some of the cases are confounded by concomitant vaccinations, there is sufficient evidence of a causal association to amend the product information to include these side effects with a frequency of "unknown" in section 4.8 of the SmPC and to add a warning to section 4.4 of the SmPC for appropriate medical treatment to be in place in case of an anaphylactic event. The Package Leaflet was updated accordingly. In addition the product information was updated in line with the QRD template version 8.
IB/0038/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	25/07/2012	n/a		
II/0037	Change in the manufacturer of a reagent	19/07/2012	19/07/2012		

	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product				
IG/0156	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	24/02/2012	n/a		
II/0031	To extend the upper limit of the administration of the third dose of vaccine from up to 26 weeks to up to 32 weeks of age. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to amend the section on Braille in the Labelling in line with current guidance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	19/01/2012	21/02/2012	SmPC, Labelling and PL	Please refer to the scientific discussion of the Assessment Report Rotateq-H-669-II-31-AR.
IB/0033	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	18/11/2011	n/a		
IA/0032	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate	12/08/2011	n/a		

	from an already approved manufacturer				
R/0029	Renewal of the marketing authorisation.	17/03/2011	18/05/2011	SmPC, Annex II, Labelling and PL	The CHMP is of the opinion that the renewal can be granted with unlimited validity.
IG/0059/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	15/04/2011	n/a		
II/0030	Update of Summary of Product Characteristics. To update sections 4.4 (Special warnings and precautions for use) and 4.8 of the SmPC regarding intussusception following a request by CHMP in December 2010. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/02/2011	08/04/2011	SmPC	Based on surveillance data form Australia, which pointed towards a small increased risk of intussusception during the first week after the first dose of Rotateq, and the power of the pre-licensure trials, study P019, and the a further study carried out using the CDC's Vaccine Safety Datalink data (VSD), an increased relative risk of IS of less than 5 within 7 days of vaccination cannot be excluded. The Product information was therefore updated to include intussusception as an adverse event identified through post-marketing surveillance in section 4.8 of the SmPC and section 4.4 was updated to state the following: No increased risk of intussusception was observed in clinical trials following administration of RotaTeq when

					compared with placebo. However, a small increased risk of intussusception in the 31-day period, mostly within 7 days following the administration of the first dose of RotaTeq, cannot be excluded. Therefore, 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). Parents/guardians should be advised to promptly report such symptoms.
II/0026/G	This was an application for a group of variations. This was an application for a group of variations. Update of SmPC Section 4.9 "Overdose" to reflect post-marketing reports of overdosage. The MAH also took the opportunity of this variation to implement the new SmPC guideline (A Guideline on SmPC, September 2009). The MAH also took the opportunity to update the list of local representatives in the PL. The serology of the Rotavirus strains has been specified as per the Vaccine Working Party (VWP) recommendation on Taxonomy following the meeting of 31st of March 2009 (adopted at CHMP). Of note, the serology type for Rotavirus has also been corrected in the labelling and package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a	20/01/2011	28/02/2011	SmPC, Labelling and PL	This variation amended section 4.9 based on post authorisation reports of overdose, of which the majority were reported was an inadvertent exposure. Overall, in the remaining reports of higher than recommended doses of RotaTeq the adverse event profile reported with regard to overdose was comparable to that observed with recommended doses of RotaTeq. Furthermore, the Product information was updated in line with the latest QRD template and Vaccine Working Party recommendations for Rotavirus Taxononmy.

	PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
II/0027	Update of SmPC section 5.1" Pharmacodynamic properties", to reflect study data on vaccine effectiveness. The MAH also took the opportunity to implement template change in Annex IIB (deletion of the version number of the DDPS). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	27/01/2011	Annex II	The MAH sought to update section 5.1 of SmPC based on the results of a MAH-sponsored post-marketing study to assess the effectiveness of the vaccine in real life practice. In addition, results from a study of a vaccination campaign for infants on the hospitalisations for Rotavirus Acute Gastroenteritis: Prospective study on the urban community of Brest, France (IVANHOE study), are also being included in the same section of the SmPC.
A20/0025	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 10 May 2010 , the opinion of the CHMP on measures necessary to ensure the quality of the above mentioned medicinal product further to the detection of non-pathogenic viral strains of porcine circovirus DNA in RotaTeq and to review its impact on the risk-benefit balance.	23/09/2010	21/01/2011	SmPC	Please refer to the scientific discussion of the Assessment Report Rotateq-H-669-A20-25-AR.
IB/0028	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	17/12/2010	n/a		

II/0024	Update of the Summary of Product Characteristics (SmPC) to reflect recent changes in the Company Core Datasheet (CCDS) with respect to SmPC Sections 4.4 concerning transmission of vaccine virus strains and 4.8 to add gastroenteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency Disease (SCID). The MAH also took the opportunity to clarify section 4.1 "Therapeutic indications" to better reflect section 4.2 "Posology and method of administration" The MAH also took the opportunity to implement the new QRD templates in the SmPC and PL, to reflect the status of the Risk Management Plan in Annex II and to amend the list of local representatives in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/06/2010	06/08/2010	SmPC, Annex II and PL	Based on data submitted with this variation the MAH sought to update SmPC section 4.4 concerning transmission of vaccine virus strains following a published case report describing transmission of vaccine-type reassortant rotavirus to an un-immunised primary contact. The PI was updated to reflect the findings from this case. In addition the CHMP agreed to amend SmPC section 4.8 to be in line with the wording on SCID in SmPC section 4.4 and to include the additional changes to the PI outlined in the scope.
II/0022	To revise sections 4.8 and 5.1 of the SmPC based on results of a post marketing safety surveillance (study 019). The results of study 019 utilised medical claims data from a large insured population in the US to assess the risk of intussusception, Kawasaki Disease and other health outcomes requiring emergency services or hospitalisation in infants receiving RotaTeq. Update of Summary of Product Characteristics	18/02/2010	30/03/2010	SmPC	In summary, the results indicate a lack of statistically significant elevated risk of either intussusception or Kawasaki disease associated with vaccination with RotaTeq. The Safety Monitoring Committee set up for this study noted that the evidence reviewed with respect to intussusception, Kawasaki Disease, and general safety continued to support the safety of RotaTeq. Therefore, the results of this study do not change the conclusion that the risk-benefit relationship for approved use of RotaTeq remains favourable. The study findings were generally considered reassuring with respect to the overall safety of

					RotaTeq and any risk of IS or KD. Nevertheless, the Produc Information was updated as a precautionary measure to inform about the current status of the scientific knowledge on KD and IS in view of rotavirus vaccination.
IA/0023/G	This was an application for a group of variations. To change in the name of the Drug substance and drug product manufacturer. Following the merger between Merck & Co., Inc. and Schering-Plough Corporation, the name of the company has changed from Merck & Co., Inc. to Merck Sharp & Dohme Corp. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	25/03/2010	n/a	Annex II	
II/0021	Update of the detailed description of pharmacovigilance system (DDPS) including the change of the Qualified Person Responsible for Pharmacovigilance (QPPV). The version number of the DDPS in Annex II has been updated accordingly. Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II	The DDPS has been updated to version 2.0 in order to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements

II/0020	Update of section 4.4 'Special warnings and precautions for use' of the Summary of Product Characteristics (SPC) for RotaTeq vaccine to reflect post-marketing cases of gastroenteritis associated with vaccine virus, in infants with severe combined immunodeficiency (SCID). Update of Summary of Product Characteristics	24/09/2009	23/10/2009	SmPC	During routine safety review by the MAH, three reports of infection with a vaccine strain of rotavirus in immunocompromised individuals following vaccination with rotavirus vaccine, live, oral, pentavalent were identified in the MAH's Adverse Event database, for the time period starting from the IBD (28 November 2005) through 28 May 2009. All 3 reports were received from healthcare providers. The adverse events contained in these reports are not reflected in the current section 4.4 'Special warnings and precautions for use' of the SPC. Therefore, the MAH submitted this variation to update the SPC to include a warning for the use of RotaTeq vaccine in patients with SCID.
II/0016	Update of Summary of Product Characteristics. To amend section 4.5 of the SPC to update existing information on the concomitant use of RotaTeq with Infanrix hexa based on a clinical comparative study in healthy infants that evaluated the safety and efficacy of concomitant administration of RotaTeq and Infanrix hexa. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	29/06/2009	SmPC and PL	A clinical comparative study in healthy infants that evaluated the safety and efficacy of concomitant administration of RotaTeq and Infanrix hexa showed that co-administration of RotaTeq with DTaP-IPV-HBV-Hib vaccine (Infanrix hexa) at approximately 2, 3, and 4 months of age did not affect the immune responses and the safety profiles of the co-administered vaccines compared to separate administrations. This information was included in the SPC.
II/0015	Update of Summary of Product Characteristics and Package Leaflet To update section 4.5 of the SPC to include information on the concomitant use of RotaTeq with meningococcal group C conjugate vaccine based on	29/05/2009	29/06/2009	SmPC and PL	The update of section 4.5 of the SPC was based on an open-label, randomised, multicentre study designed as a comparative, sequential versus concomitant administration study to evaluate the safety and immunogenicity of concomitant use of RotaTeq and meningococcal group C

	clinical trial data on healty infants from an open-label, randomised, comparative study on the immunogenicity and safety of the concomitant use of RotaTeq with a meningococcal group C conjugate vaccine. The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				conjugate (MenCC) vaccine in healthy infants. For this study, 247 infants at about 7 months of age were randomised either to a group that received the meningococcal serogroup C conjugate vaccine (MCC vaccine) concomitantly with the first and second doses of RotaTeq (concomitant administration group) or a group that received MCC vaccine and RotaTeq at separate visits (Sequential administration group). Most infants in both groups also received DTaP-IPV-Hib vaccine during the study. Concomitant administration of RotaTeq and MenCC at about 3 and 5 months did not affect the immunogenicity of either vaccine. Concomitant administration resulted in a higher rate of local and systemic Adverse Events compared to separate administration, but this difference was not enough to preclude co-administration. The Product Information was therefore updated to reflect these findings.
IA/0019	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	25/03/2009	n/a		
IA/0018	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	17/12/2008	n/a		
IA/0017	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	17/12/2008	n/a		
II/0013	To update sections 4.4 and 5.1 of the SPC to include additional data from an extension of the pivotal REST study on the reduction in the rate of hospital admissions and emergency department visits associated with confirmed episodes of rotavirus	25/09/2008	28/10/2008	SmPC and PL	Additional efficacy data were collected during an extension study of the pivotal REST study. This was conducted only at clinical sites in Finland (i.e. the Finnish Extension Study [FES]). FES was not performed under an amendment to the protocol for REST but as an add-on, although using the

	gastroenteritis (RVGE) during a period of up to 3 years following vaccination with RotaTeq. The PL is updated accordingly. In addition, the MAH took the opportunity to reflect the class wording on apnoea in the PL as requested by the CHMP in July 2008 and to amend the contact details of the local representatives in Denmark and Malta in the PL. Update of Summary of Product Characteristics and Package Leaflet				same approach to case identification. The analyses covered the efficacy of RotaTeq with regard to health care encounters for hospitalisation and emergency department visits for a period of up to 3 years after completion of the 3-dose vaccination regimen based on data from REST and the FES combined. Since the duration of protection after completion of the 3 dose vaccination series has now been studied beyond the second issue, the warning was deleted. The product information was updated to include the results which showed that the reduction up to 3 years post-vaccination in the rate of hospitalisations and emergency department visits for RV gastroenteritis was 94.4% for serotypes G1-G4, 95.5% for serotype G1, 81.9% for serotype G2, 89.0% for serotype G3, 83.4% for serotype G4, and 94.2% for serotype G9. Further to the SPC update regarding the potential risk of apnoea in very premature infants, the PL was updated to inform that in babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination.
II/0012	To update section 5.1 of the Summary of Product Characteristics (SPC) to include results of post-hoc analyses of data from the pivotal safety and efficacy study 006 (REST study) on the efficacy of the vaccine between doses 1 and 2 and between doses 2 and 3. Update of Summary of Product Characteristics	25/09/2008	28/10/2008	SmPC	Data obtained from a retrospective analysis of the pivotal safety and efficacy study 006 (Rotavirus Efficacy and Safety Trial (REST)) showed that some reduction in the numbers of cases of severe rotavirus gastroenteritis could be achieved with less than three doses, however the data did not support a recommendation for a 2-dose schedule. Therefore, this information was included in section 5.1 of the SPC as additional information.

II/0014	Change(s) to the manufacturing process of the finished product. Change(s) to the manufacturing process for the finished product	25/09/2008	01/10/2008		
II/0011	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.8 of the SPC with information on the adverse events 'urticaria' and 'haematochezia' as requested by the CHMP following the assessment of the 3rd PSUR (covering the period 28.11.06 - 27.05.07). The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/03/2008	23/04/2008	SmPC and PL	Since Rotateq was placed on the market up to March 2007, 8 cases of urticaria (hives) were reported. In a clinical trial with Rotateq, the rate of 'haematochezia' (blood in the stool) was comparable between infants who received the vaccine and those who received a placebo (0.6%). However, 76 spontaneous reports of 'haematochezia' were received during the period covered by the 3rd PSUR. Therefore, these two adverse events have been included in the SPC as reported post-marketing.
II/0009	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.2, 4.4, and 5.1 of the Summary of Product Characteristics (SPC) regarding administration of Rotateq to prematurely born infants based on data from a clinical trial. The Package Leaflet was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	15/11/2007	14/12/2007	SmPC and PL	The CHMP found no reasons on grounds of safety to preclude the administration of RotaTeq to infants born at a gestational age of at least 25 weeks. These infants are prone to more severe illness if they do contract rotavirus gastroenteritis and so, taking into account the efficacy data, the overall risk-benefit relationship is considered to be favourable. Most of the data assessed came from infants born at a gestational age of at least 28 weeks (the majority being 32 weeks or more at birth) with very few aged 25-28 weeks.
II/0010	Update of sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the Summary of Product Characteristics to	15/11/2007	11/12/2007	SmPC	Following a review on the risk of apnoea in very premature infants after immunisation the CHMP recommended a class labelling on apnoea for all vaccines in very premature

	implement the class labelling text on the risk of apnoea following vaccination of very prematurely born infants agreed by the CHMP in July 2007. Update of Summary of Product Characteristics				infants. The SPC was updated to include information about the potential risk of apnoea and the need for respiratory monitoring for 48-72h, when the primary immunisation series is administered to very premature infants (born ? 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. Nonetheless, preterm infants should not be withdrawn from the immunisation scheme because the benefit of vaccination outweighs the risk of apnoea.
IB/0008	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	17/09/2007	n/a		
II/0007	Update of SPC to include Kawasaki Disease in section 4.8 of the SPC according to a request from CHMP in May 2007 following the assessment of cases of Kawasaki Disease observed in a clinical study Update of Summary of Product Characteristics	19/07/2007	07/09/2007	SmPC	During the Phase III "Rotavirus Efficacy and Safety Trial" (REST) assessed for the initial Marketing Authorisation of RotaTeq, 3 cases of Kawasaki Disease (KD) were reported after the use of RotaTeq, which was not considered a safety signal at that time. After the unblinding of two further cases, there were in total 5 cases of KD that developed in children receiving RotaTeq. This compares with one case in a child receiving placebo, a risk difference that was not significant. However, as the study was not sufficiently powered to investigate KD, an increase the risk of KD in association with RotaTeq could not be excluded with any degree of certainty. As such the CHMP considered it necessary due to the above reasons and the rarity of this condition, to reflect this data in the Product Information.
II/0005	To amend section 4.5 of the Summary of Product Characteristics (SPC) to include the concomitant	21/06/2007	24/07/2007	SmPC, Labelling and	Following the assessment of a randomised open label study that was conducted in Latin America comparing the safety

	administration of RotaTeq and Oral Poliovirus Vaccine (OPV). The Package Leaflet (PL) was updated accordingly. The MAH took the opportunity to introduce the local representatives for Bulgaria and Romania and to change the contact details of the local representatives of Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Portugal and Slovenia. Furthermore, the MAH introduced small corrections in the Labelling and PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet			PL	and immunogenicity of concomitant and staggered administration of RotaTeq and OPV, the CHMP concluded that the staggered (vaccination of OPV followed by a dose of RotaTeq or RotaTeq followed by OPV within 2-6 weeks) and the concomitant administration were comparable in terms of immunogenicity and safety. The co-administration of RotaTeq and OPV did not interfere with the immunogenicity of each of the poliovirus types 1, 2, or 3. Concomitant administration of OPV may reduce some immune responses to rotavirus vaccine but there is evidence that the immune response generated still results in a high level of efficacy against severe rotavirus gastro-enteritis. The Product Information was therefore updated accordingly.
IA/0006	IA_06_a_Change in ATC code: Medicinal products for human use	18/06/2007	n/a	SmPC	
II/0004	Change(s) to shelf-life or storage conditions	22/03/2007	28/03/2007		
IA/0002	IA_37_a_Change in the specification of the finished product - tightening of specification limits	08/09/2006	n/a		
IB/0001	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	25/08/2006	n/a		