Simulect

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
IB/0116/G	This was an application for a group of variations. B.II.e.5.z - Change in pack size of the finished product - Other variation B.II.e.5.z - Change in pack size of the finished product - Other variation	09/10/2023		SmPC, Labelling and PL	

[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).

IA/0117/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 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)	05/10/2023	n/a		
IB/0115/G	This was an application for a group of variations. B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a	15/09/2022	n/a		

	biological/immunological medicinal product				
II/0114/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.II.h.1.b.2 - Update to the Adventitious Agents Safety Evaluation information - Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier - without modifications of risk assessment B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS -	08/09/2022	n/a		

	Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol B.I.e.4.a - Changes to an approved change management protocol - Major changes B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS				

IB/0113	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	07/12/2021	n/a		
PSUSA/301/202104	Periodic Safety Update EU Single assessment - basiliximab	02/12/2021	n/a		PRAC Recommendation - maintenance
IB/0112	B.II.d.2.z - Change in test procedure for the finished product - Other variation	26/10/2021	n/a		
N/0111	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/09/2021	29/11/2021	PL	
IAIN/0109	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	22/06/2021	29/11/2021	Annex II and PL	
IB/0108	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/12/2020	29/11/2021	SmPC, Annex II, Labelling and PL	
II/0107	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	03/12/2020	n/a		
IA/0106/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.c.2.a - Change in the specification parameters and/or limits of the immediate packaging of the AS -	16/07/2020	n/a		

	Tightening of specification limits				
IAIN/0105	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	13/03/2020	30/09/2020	Annex II and PL	
II/0101/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.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.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation 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	16/01/2020	n/a		
IB/0104	B.II.b.z - Change in manufacture of the Finished Product - Other variation	20/12/2019	n/a		

IB/0103	B.II.a.z - Change in description and composition of the Finished Product - Other variation	09/12/2019	n/a		
IA/0102	A.7 - Administrative change - Deletion of manufacturing sites	06/09/2019	30/09/2020	Annex II	
IB/0099	B.II.a.z - Change in description and composition of the Finished Product - Other variation	15/05/2019	n/a		
IB/0098/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch	14/05/2019	n/a		

	size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
IB/0100	B.II.b.z - Change in manufacture of the Finished Product - Other variation	15/04/2019	n/a		
PSUSA/301/2	Periodic Safety Update EU Single assessment -	29/11/2018	n/a		PRAC Recommendation - maintenance

01804	basiliximab				
IB/0097/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.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	13/09/2018	n/a		
IB/0095/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/06/2018	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.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.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test				

	procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
T/0094	Transfer of Marketing Authorisation	26/03/2018	12/04/2018	SmPC, Labelling and PL	
IB/0093	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	04/08/2017	n/a		
IB/0092	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	03/03/2017	n/a		
IB/0091	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	22/02/2017	19/02/2018	SmPC, Annex II, Labelling and PL	
IB/0090/G	This was an application for a group of variations.	18/03/2016	n/a		

	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.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 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 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 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 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 B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
IB/0089	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	16/03/2016	n/a		

IB/0088/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	10/12/2015	n/a		
PSUSA/301/201504	Periodic Safety Update EU Single assessment - basiliximab	03/12/2015	n/a		PRAC Recommendation - maintenance
II/0086	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	23/04/2015	n/a		
IAIN/0084	A.1 - Administrative change - Change in the name and/or address of the MAH	28/11/2014	19/11/2015	SmPC, Labelling and PL	

IB/0085/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	27/11/2014	n/a		
II/0080/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.c - Changes in the manufacturing process of	20/11/2014	n/a		

	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 B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits				
IB/0083/G	This was an application for a group of variations.	17/10/2014	n/a		

	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0078	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	04/09/2014	SmPC	
IA/0081	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	15/08/2014	n/a		
IB/0082	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	12/08/2014	n/a		
IB/0079	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	16/07/2014	n/a		
IB/0077	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	22/05/2014	n/a		

IB/0076/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.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	30/04/2014	n/a		
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/01/2014	04/09/2014	PL	
IA/0075/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) B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	13/12/2013	n/a		
II/0073/G	This was an application for a group of variations. changes to the manufacturing process of the active substance	24/10/2013	n/a		

	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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
II/0072	change in the manufacturing process of the active substance 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	24/10/2013	n/a		
IA/0071/G	This was an application for a group of variations.	06/08/2013	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0070	A.7 - Administrative change - Deletion of manufacturing sites	30/07/2013	n/a		
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
II/0068	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	21/06/2012	06/07/2012	Annex II	
IA/0067/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a	14/02/2012	n/a		

	manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
II/0066/G	This was an application for a group of variations. - Change of the manufacturer of the active substance - Changes in the manufacturing process of the active substance - Changes to in-process tests or limits applied during the manufacture of the active substance - Changes in specification parameters and/or limits of reagents used in the manufacture of the active substance 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 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 medicinal product and is not related to a protocol B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	15/12/2011	30/01/2012	Annex II	

	material/intermediate/reagent - Other variation				
II/0065	Update of sections 4.4 and 4.8 of the SmPC to align the information presenting symptoms of hypersensitivity reactions and to revise the frequency category for "Immune system disorders" identified based on post-marketing reports. The package leaflet is updated accordingly. Section 4.4 of the SmPC is also updated to harmonise the warning statements on "neoplasms and infections" with those in section 4.8. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	14/12/2011	SmPC and PL	The cautionary statement regarding hypersensitivity reactions has been revised in order to harmonise the characterisation of symptoms of hypersensitivity reactions in sections 4.4 and 4.8 of the SmPC. A reliable enumeration of the frequency of hypersensitivity reactions based on reports from the post-marketing setting was almost impossible, due to the suspected high rate of under-reporting. The MAH therefore proposes to delete the sentence related to the frequency of the events in section 4.4 and to propose the following statement in section 4.8: "Because these reactions are reported voluntary from a population of uncertain size, it is not always possible to reliably estimate their frequency. Based on data from clinical trials, the overall incidence and profile of viral, bacterial and fungal infections amongst patients using dual or triple immunosuppressive therapy was similar in Simulect (75.9%) and placebo treated groups. The same was true for the rate of opportunistic infections, such as CMV infections (14.6% vs. 17.3%). A statement regarding the incidence of opportunistic infections as reported from clinical trials was therefore added to section 4.4, to bring the wording in line with statements in section 4.8.
II/0064	Update of section 4.8 of the SmPC by adding "cardiac failure" and "myocardial infarction" to specify the information regarding cardiac-related disorders leading to death in patients using Simulect. C.I.4 - Variations related to significant modifications	20/10/2011	14/12/2011	SmPC	The review of the results from the two four-year extensions to studies CHIB 201 and CHIB 352 revealed that cardiac failure and myocardial infarction were the main causes for cardiac-related disorders leading to death. The MAH therefore intends supplemented the medical definitions "cardiac failure" and "myocardial infarction" to the term

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				"cardiac-related disorders" for clarification.
II/0063	Update of section 4.4 of the SmPC to add a cautionary statement regarding the use of live and inactivated vaccines in immunosuppressed patients. The package leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	14/12/2011	SmPC and PL	So far, no specific data on the concomitant use of Simulect and vaccination is available. However, vaccination guidelines for immunocompromised patients display that the application of live-virus vaccines was not recommended due to the risk of uninhibited viral replication. Moreover, there is only little evidence from literature that the administration of live-virus vaccines in solid organ transplant recipients was safe. Prospective studies would be impossible due to ethical considerations. In contrast, the administration of approved inactivated vaccines according to the schedules for the general population are consistently considered safe in patients after organ transplantation and have not been found as being associated with vaccination related adverse events or with the induction of transplant rejections. Though, response to vaccination might be reduced in immunocompromised patients. Therefore, the inclusion of information reflecting current data available on the use of live and inactivated vaccines in immunocompromised patients in the Simulect EU SmPC is endorsed by the CHMP.
II/0062/G	This was an application for a group of variations. Change in test procedure for starting materials used in the manufacturing process of the active substance. B.I.b.2.d - Change in test procedure for AS or	22/09/2011	22/09/2011		

	starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS				
IB/0060	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	01/09/2011	n/a		
IA/0061	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	15/07/2011	n/a	Annex II and PL	
IG/0065	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	17/05/2011	n/a		
II/0059	Change to in -process tests or imits applied during the manufacture of the finished product B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the	17/03/2011	04/04/2011		

	finished product				
II/0057	Update of section 5.1 of the SmPC with results from a clinical study in paediatric renal transplant recipients (DE01) as requested by the CHMP further to the assessment of FU2 033.1. In addition the PI is brought in line with latest QRD template and the list of the local representatives in the PL is amended. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/02/2011	18/03/2011	SmPC and PL	At the CHMP's request the MAH has included the results of study DE01 in the Simulect's SmPC. Apart from deficiencies in the clinical trial conduct and analysis one major problem is the lack of understanding of the relevance of "borderline" changes in the biopsies. Exclusion of borderline cases from the definition of acute rejection leads to clearer benefit of basiliximab therapy, inclusion of borderline cases decreases the differences between both treatment arms. Of note, inclusion of borderline cases and analysing the Kaplan-Meier curves for the primary composite endpoint (survival, graft survival, acute rejection) show merely a delay of events and an aligning of the curves at a later time point. The safety is difficult to evaluate as multiple confounding factors are present in this patient population. The CHMP agrees that the data in summary indicate that basiliximab may reduce the rate of acute biopsy proven rejection but a proof is lacking. It also remains unclear whether the assumed reduction of biopsy proven rejection translates into a longer lasting benefit for the patient. This is similar to the situation in adults but the prevention of acute rejections has been accepted as a treatment goal in itself since it is associated with a better long term outcome. Taken together the benefit risk balance appears to be similar in children and adults.
II/0056/G	This was an application for a group of variations. To change to the manufacturing process, to tighten specification limits, to tighten in process controls limits and minor change to an approved test	17/02/2011	28/02/2011		

	procedure 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 medicinal product and is not related to a protocol 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 medicinal product and is not related to a protocol B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0058	B.II.b.2.a - Change to batch release arrangements	09/02/2011	n/a		

	and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
IB/0055	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	10/01/2011	n/a		
II/0054	Update of the fished product testing. Change(s) to the manufacturing process for the finished product	19/11/2009	08/12/2009		
II/0053	Update of the active substance testing. Change(s) to the test method(s) and/or specifications for the active substance	19/11/2009	08/12/2009		
II/0052	Change to the active substance manufacturing process. Change(s) to the manufacturing process for the active substance	19/03/2009	25/03/2009		
II/0051	Change of the culture medium component in the active substance manufacturing process. Change(s) to the manufacturing process for the active substance	19/03/2009	25/03/2009		

II/0050	Minor change in the cell culture medium during the manufacture of the active substance Change(s) to the manufacturing process for the active substance	23/10/2008	27/10/2008		
R/0049	Renewal of the marketing authorisation.	21/08/2008	08/08/2008	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of Simulect continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Simulect continues to be favourable.
IA/0048	IA_06_a_Change in ATC code: Medicinal products for human use	04/03/2008	n/a	SmPC	
II/0047	Change(s) to the manufacturing process for the active substance	20/09/2007	01/10/2007		
II/0046	Change(s) to the manufacturing process for the active substance	20/09/2007	01/10/2007		
II/0044	Update of sections 4.4 and 4.8 of the SPC with information on reported opportunistic infections and lymphoproliferative disorders, as requested by the CHMP on 24 January 2007 further to assessment of PSUR 11 (covering the period from 01 May 2005 to 30 April 2006). The MAH also took the opportunity to bring section 2 of the Package Leaflet in line with the SPC regarding the contraindication of Simulect in pregnancy and lactation. Furthermore, the annexes	24/05/2007	09/07/2007	SmPC, Annex II, Labelling and PL	Following the assessment of PSUR 11 (covering the period from 01 May 2005 to 30 April 2006) and the subsequent responses by the MAH, the CHMP considered that the current wording of the SPC could lead to an underestimation of the risk for developing opportunistic infections and lymphoproliferative disorders and a revision of the SPC was recommended. As a result, within this variation, the statements considered as misleading were removed from sections 4.4 and 4.8. Furthermore,

	have been updated according to the latest EMEA/QRD template. Minor linguistic corrections have also been made to the Estonian SPC and the Greek labelling. Update of Summary of Product Characteristics, Labelling and Package Leaflet				"lymphoma" and "cytomegalovirus" have been mentioned as examples of respectively, lymphoproliferative disorders and opportunistic infections reported with Simulect as part of an immunosuppressive regimen in kidney transplantation. In addition, section 2 of the Package Leaflet was updated in accordance with the SPC in order to clearly reflect the contraindication of Simulect in pregnancy and lactation.
II/0042	Change(s) to the manufacturing process for the finished product	21/06/2007	28/06/2007		
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/05/2007	n/a	PL	
II/0041	Update of sections 4.9 and 5.3 of the SPC to reflect the results of a repeat-dose toxicity study. Section 4.8 of the SPC is updated in line with the frequency and system organ class MedDRA terminology. Minor linguistic changes were introduced in the SPC, Labelling or Package Leaflet for some EU languages, as relevant. Update of Summary of Product Characteristics, Labelling and Package Leaflet	14/12/2005	31/01/2006	SmPC, Labelling and PL	
II/0040	To update of section 4.4 "Special warnings and special precautions for use" of the Summary of Product Characteristics (SPC) to strengthen the warnings on hypersensitivity reactions at re-exposure to Simulect, following an internal review of the existing safety data. The "cytokine release	26/05/2005	08/07/2005	SmPC, Annex II, Labelling and PL	

	syndrome" is being added to section 4.8 "Undesirable effects" with consequent update of section 5.1 "Pharmacodynamic properties". Relevant sections of the Package Leaflet (PL) are amended in accordance. In addition the relevant sections of the SPC, labelling, PL and Annex II will be updated in line with the latest EMEA QRD templates. Furthermore, minor linguistics changes to the Czech, Danish, Estonian, French, German, Greek, Hungarian, Icelandic, Italian, Latvian, Lithuanian, Norwegian, Polish, Portuguese, Slovak, Slovenian, Spanish and Swedish, Greek, Estonian SPC, Labelling and PL, as relevant. Update of Summary of Product Characteristics, Labelling and Package Leaflet				
II/0035	Change(s) to the manufacturing process for the active substance	15/12/2004	21/12/2004		
IB/0039	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	15/12/2004	n/a		
IB/0036	IB_26_b_Change in the specification of immediate packaging - addition of new test parameter	10/11/2004	n/a		
IB/0038	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	09/11/2004	n/a		
N/0034	Minor change in labelling or package leaflet not	03/05/2004	n/a	PL	

	connected with the SPC (Art. 61.3 Notification)				
R/0033	Renewal of the marketing authorisation.	24/07/2003	20/10/2003	Annex II	
I/0032	01_Change in the name of a manufacturer of the medicinal product	15/04/2003	04/06/2003	Annex II and PL	
II/0031	Changes in sections 4.4, 4.8 and 5.1 of the SPC to include the long-term data of the pivotal studies CHIB 201-E-01 and CHIB 352-E-01 (particularly the five year safety and the general efficacy, further to the request of the CPMP on June 2002). Moreover, inclusion of QRD comments to the SPC, PL and Labelling as previously in Simulect 10mg line extension. In addition, inclusion of minor corrections in section 4.8 of both strengths in line with the Core Data Sheet.Finally, inclusion of linguistic corrections to the Italian 20mg strengths SPC and PL. Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	23/05/2003	SmPC, Labelling and PL	In April 2002, the results of the 5-year extension pivotal studies CHIB201E and CHIB352E were submitted by the MAH as one of the two clinical post-marketing follow-up measures requested by the CPMP at the time of the opinion of the initial Marketing Authorisation. The aim of these studies was to collect information about the graft and patients survival up to five years after transplantation. Long-term chronic graft failure is still a matter of concern after renal transplantation. Acute rejection episodes are an important risk factor for chronic rejection and graft loss. In section 5.1 (Pharmacodynamic properties) of the SPC, the following changes were endorsed by the CPMP: "Clinical studies:(_)In a pooled analysis of two five-year open-label extension studies (586 patients total) the combined graft and patient survival rates were not statistically different for the Simulect and placebo groups. Extension studies also showed that patients who experienced an acute rejection episode during the first year after transplantation experienced more graft losses and deaths over the five-year follow-up period than patients who had no rejection. These events were not influenced by Simulect .
X/0026	The new strength, 10 mg powder and solvent for solution for injection/infusion, is indicated for the treatment of adult and paediatric patients. The 10	21/11/2002	07/03/2003	SmPC, Annex II, Labelling	The data submitted in support of the application demonstrated production consistency, stability and quality of Simulect 10 mg. Except for the fill volume and filling

	mg strength is identical to the already licensed 20 mg strength with regard to the qualitative and percentage quantitative composition, and the primary packaging material. The ampoule for the solvent, water for injection, is the same as for the 20 mg strength, but only 2.5 ml water for injection have to be withdrawn for the reconstitution of the 10 mg strength. X-3-iii_Addition of new strength			and PL	step, the manufacturing process and controls and specifications for the active substance and finished product remain unchanged with reference to the authorised 20 mg strength. Since a change from 20 mg to 10 mg is not expected to affect the toxicological and clinical profile of the medicinal product, new toxicological and clinical data were not submitted and this was considered acceptable. Overall the risk/benefit profile was considered unchanged and a positive opinion was adopted for the new 10 mg strength.
II/0028	Change(s) to the test method(s) and/or specifications for the active substance	17/10/2002	25/10/2002		
II/0029	Change(s) to the test method(s) and/or specifications for the finished product	19/09/2002	25/09/2002		
I/0027	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	21/08/2002	18/09/2002		
I/0021	12_Minor change of manufacturing process of the active substance	15/11/2001	27/02/2002		
I/0020	12_Minor change of manufacturing process of the active substance	15/11/2001	27/02/2002		
I/0025	26_Changes to comply with supplements to pharmacopoeias	18/10/2001	14/02/2002		
I/0023	15_Minor changes in manufacture of the medicinal product	18/10/2001	14/02/2002		

	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process				
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/01/2002	02/04/2002	PL	
I/0024	26_Changes to comply with supplements to pharmacopoeias	18/10/2001	n/a		
I/0019	01_Change following modification(s) of the manufacturing authorisation(s)	25/01/2001	11/03/2001		
I/0018	20_Extension of shelf-life as foreseen at time of authorisation	25/01/2001	n/a	SmPC and PL	
I/0017	20a_Extension of shelf-life or retest period of the active substance	25/01/2001	n/a		
II/0016	Update of Summary of Product Characteristics, Labelling and Package Leaflet	26/07/2000	01/12/2000	SmPC, Labelling and PL	
II/0015	Update of Summary of Product Characteristics and Package Leaflet	26/07/2000	01/12/2000	SmPC and PL	
II/0014	Update of Summary of Product Characteristics and Package Leaflet	26/07/2000	01/12/2000	SmPC and PL	
II/0013	Update of Summary of Product Characteristics and Package Leaflet	12/04/2000	11/07/2000	SmPC and PL	

I/0012	25_Change in test procedures of the medicinal product	16/02/2000	17/05/2000		
I/0011	24_Change in test procedure of active substance	16/02/2000	17/05/2000		
I/0010	24_Change in test procedure of active substance	16/02/2000	17/05/2000		
I/0009	15_Minor changes in manufacture of the medicinal product 16_Change in the batch size of finished product 01_Change following modification(s) of the manufacturing authorisation(s)	16/02/2000	17/05/2000		
I/0007	20_Extension of shelf-life as foreseen at time of authorisation	12/11/1999	08/02/2000	SmPC	
I/0008	20a_Extension of shelf-life or retest period of the active substance	12/11/1999	n/a		
I/0001	20_Extension of shelf-life as foreseen at time of authorisation	26/05/1999	29/07/1999	SmPC	
I/0005	17_Change in specification of the medicinal product	24/06/1999	n/a		
I/0004	14_Change in specifications of active substance	24/06/1999	n/a		
I/0003	24_Change in test procedure of active substance	24/06/1999	n/a		
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/05/1999	29/07/1999	PL	

I/0002	20a_Extension of shelf-life or retest period of the active substance	26/05/1999	n/a		