Synagis

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
II/0132	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update safety information based on results from safety data evaluations from multiple sources, including the clinical Study W00-350, post-Marketing Clinical Surveillance Programme (REACH), literature searches and the AstraZeneca Global	14/09/2023		SmPC and PL	As a result of this variation, the following text now appears in section 5.1 of the SmPC: "In an open label prospective trial pharmacokinetics and immunogenicity were evaluated after administration of 6 doses of palivizumab within a single RSV season. The pharmacokinetic data indicated that adequate mean

[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).

	Patient Safety database. The MAH took the opportunity to change the details of the Local Representatives in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				palivizumab levels were achieved in all 14 children for whom data on 30 day through serum concentrations after the sixth dose were available (see section 5.2). No significant elevations of anti-palivizumab antibody titer were observed in these 14 participants. Transient, low levels of anti palivizumab antibody were observed in one child after the second dose of palivizumab that dropped to undetectable levels at the fifth and seventh dose." Additionally, the following new text was included in section 5.2: "In the open label prospective trial evaluating pharmacokinetics with administration of 6 monthly intramuscular doses of 15 mg/kg of palivizumab, mean 30 day trough serum concentrations were approximately 40 □g/ml after the first dose, 120 □g/ml after the fourth dose, and 140 □g/ml after the sixth dose." The following sentence was added to Section 4.8: "In a small open label prospective trial of 14 subjects, who received 6 doses, the adverse events reported were consistent with the known safety profile of palivizumab." For more information, please refer to the Summary of Product Characteristics.
IA/0135/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	01/08/2023	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
II/0131	Submission of an updated RMP in order to remove from the list of safety concerns "Anaphylaxis, Anaphylactic shock, and Hypersensitivity" and "Medication error of mixing lyophilised and liquid palivizumab before injection". In addition, the MAH took the opportunity to apply the revised template. RMP version 2.3 is approved with this procedure. 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	14/04/2023	n/a		
IA/0134	A.7 - Administrative change - Deletion of manufacturing sites	11/04/2023	n/a		
IB/0133	B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	21/03/2023	n/a		
IB/0130	B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	14/09/2022	n/a		

IB/0129/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	14/09/2022	n/a		
IA/0128	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	13/07/2022	26/07/2023	SmPC and PL	
PSUSA/2267/ 202106	Periodic Safety Update EU Single assessment - palivizumab	13/01/2022	n/a		PRAC Recommendation - maintenance
II/0127/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.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.a.2.c - Changes in the manufacturing process of	16/12/2021	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				
IB/0125	C.I.7.a - Deletion of - a pharmaceutical form	31/08/2021	05/08/2022	SmPC, Labelling and PL	
T/0124	Transfer of Marketing Authorisation	24/02/2021	18/03/2021	SmPC, Labelling and PL	
PSUSA/2267/ 202006	Periodic Safety Update EU Single assessment - palivizumab	11/02/2021	n/a		PRAC Recommendation - maintenance
IB/0123/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)	15/12/2020	n/a		
IB/0122/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	13/11/2020	n/a		

	(including replacement or addition) B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation				
IB/0120	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/06/2020	18/11/2020	SmPC, Labelling and PL	
IB/0119	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/11/2019	18/11/2020	SmPC, Annex II, Labelling and PL	
II/0118	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	11/04/2019	n/a		
IB/0117	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	29/06/2018	n/a		
T/0116	Transfer of Marketing Authorisation	06/04/2018	08/05/2018	SmPC, Labelling and PL	
PSUSA/2267/ 201706	Periodic Safety Update EU Single assessment - palivizumab	08/02/2018	n/a		PRAC Recommendation - maintenance
IAIN/0115	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	02/02/2018	n/a		

IB/0112	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/08/2017	08/05/2018	SmPC, Annex II, Labelling and PL	
IA/0113/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)	03/08/2017	08/05/2018	Annex II	
N/0110	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/01/2016	08/05/2018	PL	
IG/0617	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	10/11/2015	n/a		
IG/0591/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH 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	24/07/2015	10/12/2015	SmPC, Labelling and PL	

	PSMF location				
II/0106	B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	23/07/2015	n/a		
N/0107	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/06/2015	10/12/2015	PL	
II/0098	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/04/2015	10/12/2015	SmPC, Labelling and PL	
PSUSA/2267/ 201406	Periodic Safety Update EU Single assessment - palivizumab	12/02/2015	n/a		PRAC Recommendation - maintenance
IB/0105/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	17/12/2014	10/12/2015	SmPC	
IB/0104	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/11/2014	n/a		

IG/0476	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	24/09/2014	n/a		
X/0095	Addition of a new pharmaceutical form Annex I_2.(d) Change or addition of a new pharmaceutical form	26/06/2014	22/08/2014	SmPC, Labelling and PL	
II/0099	Update of the section 4.9 of the SmPC with a revised maximum overdosage level. In addition, a minor correction was made in Section 2 of the PL and the local representative's contact details for Germany were updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	22/08/2014	SmPC and PL	The recommendations on overdosage have been updated with the results of a search of the MAH's global postmarketing safety database. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.
IB/0101/G	This was an application for a group of variations. 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	13/06/2014	n/a		

	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.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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.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.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.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material 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 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.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or				

	reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product 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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0100/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - 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.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.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	15/04/2014	n/a		

	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 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				
IB/0097	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/12/2013	n/a		
IB/0094/G	This was an application for a group of variations. 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 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.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	06/12/2013	n/a		

	batch control/testing takes place				
IG/0379	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	15/11/2013	n/a		
II/0093	Update of section 5.1 of the SmPC with additional information on in vitro antiviral activity and resistance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	04/12/2013	SmPC	The antiviral activity of palivizumab was assessed in a microneutralization assay in which increasing concentrations of antibody were incubated with RSV prior to addition of the human epithelial cells HEp-2. Palivizumab exhibited median EC50 values of 0.65 □g/ml and 0.28 □g/ml against clinical RSV A and RSV B isolates, respectively. In a genotypic analysis of 126 clinical isolates from 123 children who failed immunoprophylaxis, all RSV mutants that exhibited resistance to palivizumab (n=8) were shown to contain amino acid changes in this region of the F protein. At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L was identified in these 8 clinical RSV isolates, resulting in a combined resistance-associated mutation frequency of 6.3% in these patients. Analysis of 254 clinical RSV isolates collected from immunoprophylaxis-naïve subjects revealed palivizumab resistance-associated substitutions in 2 (1 with N262D and 1 with S275F), resulting in a resistance associated mutation frequency of 0.79%.
II/0092	Update of section 4.8 of the SmPC and section 4 of the package leaflet following complete re assessment of the information in this section in line with the current guidance. Throughout the SmPC and PL, the	24/10/2013	04/12/2013	SmPC and PL	The adverse reactions (ADRs) identified from the two pivotal studies (Study MI-CP018 and MI-CP048) were evaluated using a more robust method and were assigned a frequency category as specified in the September 2009

	name, Synagis, was spelled out in capital letters (SYNAGIS). This has been corrected in both the SmPC and PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				European Medicines Agency SmPC Guideline.
II/0091	Update of section 4.2 of the SmPC with an additional statement relating to reduced frequency and amounts of dose. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to amend contact details for the representative of Bulgaria, Czech Republic, Estonia, Finland, Greece, Latvia, Lithuania, Norway and Slovenia and to include contact details for the representative of Croatia. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	04/12/2013	SmPC and PL	The aim of this variation application was to introduce clarity to the posology and method of administration section of the Summary of Product Characteristics related to any potential reduced frequency and amount of dose. It should be highlighted that in the palivizumab pivotal clinical studies, the positive efficacy of Synagis was shown among children who received the full dose of 15 mg/kg monthly throughout the RSV season. This information has been added to the posology section of the Summary of product Characteristics. The benefit/risk profile for Synagis for the prophylaxis of serious RSV infection requiring hospitalization remains favourable for young children at high risk for serious RSV infection.
N/0090	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/06/2013	04/12/2013	Labelling and PL	To remove the instruction to read the package leaflet prior to use following comments made by the Agency. Furthermore the contact details of the local representatives for CS, HU, NL, PT, SK and UK were updated.
IB/0089	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	15/03/2013	n/a		

IG/0272	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/03/2013	n/a		
IB/0087	B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	06/03/2013	n/a		
II/0081	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	21/02/2013	n/a		
II/0077	Update of section 4.5 of the SmPC in order to reflect a risk of false-negative results in diagnostic tests for RSV in palivizumab-treated patients. The MAH has also updated the section on human anti-human antibody responses in section 4.8 based on a review of the available immunogenicity data. Furthermore, Annex II was brought in line with the latest QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	04/12/2013	SmPC and Annex II	A comparison of 19 commercially available diagnostic tests for respiratory syncytial virus (RSV) demonstrated that palivizumab can interfere with certain assays, which could lead to false-negative results. Information on the types of tests affected or not affected was therefore added to section 4.5. Due to its limited relevance for the disease diagnostics and clinical management of patients, no further actions were deemed necessary. In addition, the immunogenicity data from five large multicentre clinical trials were reviewed and it was concluded that the anti-palivizumab antibody response is infrequent, transient and of low titre, and that no clinical safety effect seems to be associated with the presence of anti-palivizumab antibodies. These observations are in line with the information present in the SmPC section 4.8; however the wording was updated to reflect all currently available data.

IB/0085/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.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	28/01/2013	n/a		
IB/0086	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	25/01/2013	n/a		
IB/0084	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	25/01/2013	n/a		
IB/0083	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	25/01/2013	n/a		
IB/0082	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement	25/01/2013	n/a		

	or addition of a site where batch control/testing takes place				
N/0080	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/01/2013	04/12/2013	PL	
IA/0079	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)	23/11/2012	n/a		
IAIN/0078	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	08/11/2012	04/12/2013	Annex II and PL	
T/0076	Transfer of Marketing Authorisation	24/09/2012	10/10/2012	SmPC, Labelling and PL	
IB/0075	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	01/06/2012	n/a		
IB/0074/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	04/04/2012	n/a		

	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
IB/0072	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	06/03/2012	n/a		
IA/0073	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	20/02/2012	n/a		
IB/0071	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	31/01/2012	n/a		
II/0065	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning for anaphylactic shock. The PLwas proposed to be updated in accordance. In addition, sections 4.2, 6.6 of the SmPC have been updated to reinforce information regarding the administration of the product and introduce additional instructions regarding the overfill. Annexes III.A and III.B “administrator's instructions” have been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	17/11/2011	19/12/2011	SmPC, Labelling and PL	The current product information for Synagis contains the general term "anaphylaxis." However, the MAH performed an additional analysis of reports describing events consistent with anaphylaxis, anaphylactoid-like reactions, and anaphylactic shock coincident with palivizumab administration. The MAH performed the search from 3 perspectives: published literature, clinical reports (including the development program and Phase 4 studies), and spontaneous post-marketing reports. On the basis of this analysis, information related to anaphylactic shock and the rare potential for fatal outcome has been added to the product information.

	clinical, clinical or pharmacovigilance data				
II/0064	Update of section 5.1 of the SmPC in order to update the safety information with the results of study M03-681 conducted in paediatric patients. This submission is done in fulfilment of FU2 17.6. In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Bulgaria and Romania. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	17/11/2011	19/12/2011	SmPC and PL	An extension of the indication for palivizumab in children with hemodynamically significant congenital heart disease (HSCHD) was granted based on study MI-CP048 (EMEA/H/C/257/II/13). At the time of approval, the MAH committed to perform a post marketing study (M03-681) to further assess the rates of serious infection, serious arrhythmia, and death associated with palivizumab prophylaxis in children with HSCHD. The final study report for study M03-681 was evaluated by the CHMP as part of FU2 17.6. The CHMP concluded that the results of this study indicate no increased risk of serious infections, serious arrhythmias, or death associated with palivizumab compared with matched untreated controls in young children with HSCHD. The benefit/risk profile for palivizumab for the prophylaxis of serious RSV infection requiring hospitalization remains favourable for young children with HSCHD. As requested by the CHMP, the MAH updated section 5.1 of the SmPC with information on this paediatric study.
IAIN/0070	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	14/12/2011	27/06/2012	Annex II and PL	
IA/0069	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	28/10/2011	n/a		
IA/0068	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate	28/10/2011	n/a		

	from an already approved manufacturer				
IB/0067	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	27/10/2011	n/a		
II/0063	Chnage in immediate packaging of the finished product B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	21/07/2011	13/09/2011	SmPC	
IA/0066	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/08/2011	n/a		
IA/0062	IA_01_Change in the name and/or address of the marketing authorisation holder	23/12/2009	n/a	SmPC, Labelling and PL	
II/0059	Update of section 4.8 of the SPC with a wording about thrombocytopenia and convulsion as potential undesirable effects of palivizumab therapy following assessment of PSUR 10. The MAH also takes the opportunity to make corrections to section 4.8 in the SPC regarding the frequency of apnoea, anaphylaxis, and urticaria. The PL was updated accordingly. In addition, section 4.9 was has been further	22/10/2009	24/11/2009	SmPC and PL	A cumulative review including reports of thrombocytopenia and convulsion coincident with palivizumab received from 19th June 1998 through 31st October 2008 was performed. There are 5 reports of decreased platelet count or thrombocytopenia with no apparent alternate etiology. Although a direct causal relationship between palivizumab and thrombocytopenia cannot be proven, a temporal relationship cannot be excluded. There are 19 reports of

	enhanced with a statement that overdoses as high as 60 mg/kg have been reported without untoward medical events. Update of Summary of Product Characteristics and Package Leaflet				non-febrile convulsions with no apparent alternative etiology for the event. These reports include reports from both premature infants and those with CHD. In 13 of these reports, the convulsion occurred within 24 hours of the palivizumab dose, and in 4 of these 13 reports, there was a positive rechallenge. There were 16 reports of convulsions associated with fever. In 8 reports, a cause for the fever was listed or could be deduced from the narrative. In the other 8 reports, there was no cause for the fever apart from the palivizumab therapy. The reports with no apparent alternate etiology described patients who may have had concurrent immunizations, or intercurrent illnesses, but none of these factors were reported. Although a causal relationship between palivizumab therapy and convulsions cannot be proven, there appears to be a temporal relationship between the two. Based on the analysis of these reports, section 4.8 of the SPC is updated to include thrombocytopenia and convulsions as potential undesirable effects of palivizumab. An additional correction was made to the Post-marketing section of the Synagis SPC regarding events of apnoea, anaphylaxis, and urticaria. Section 4.9 of the SPC has been further enhanced with a statement that overdoses as high as 60 mg/kg have been reported without untoward medical events.
IA/0061	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	01/09/2009	n/a		
IA/0060	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	01/09/2009	n/a		

R/0057	Renewal of the marketing authorisation.	29/05/2009	27/07/2009	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 this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that that the benefit risk profile of Synagis continues to be favorable. The CHMP recommends the renewal of the Marketing Authorisation for Synagis with unlimited validity.
IA/0058	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	15/06/2009	n/a		
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/10/2008	n/a	PL	
IA/0055	IA_05_Change in the name and/or address of a manufacturer of the finished product	19/05/2008	n/a	Annex II and PL	
II/0048	Change(s) to the manufacturing process for the active substance	13/12/2007	19/12/2007		
II/0054	Change(s) to solvent	18/10/2007	24/10/2007		
II/0049	To remove from Annex IIB the requirement to submit yearly PSURs following the assessment of the study M02-489. To amend the Product Information according to the latest EMEA/QRD template (version 7.2). Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/05/2007	21/06/2007	SmPC, Annex II, Labelling and PL	Since study M02-489 has been completed and found satisfactory by the CHMP, Annex IIB of the Product Information has been amended to remove the requirement to submit yearly PSURs. The MAH took the opportunity to amend the Product Information according to the latest EMEA/QRD template (version 7.2).

					Additionally, in line with the frequency category in the current EMEA/QRD template, since the adverse event "diarrhoea" has a frequency of 1.0%, its frequency category has been changed from "uncommon" to "common" in Table 1 "Clinical studies with premature and bronchopulmonary dysplasia paediatric populations" of section 4.8 "Undesirable effects" of the SPC. Additionally, for consistency with the information reported in section 4.8 of the SPC, some side effects (bleeding, weakness, constipation, drowsiness and hyperactivity) have been included in section 4 "Possible side effects" of the Package Leaflet.
II/0046	Change(s) to the manufacturing process for the active substance	26/04/2007	07/05/2007		
IA/0053	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	25/04/2007	n/a		
IA/0052	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	25/04/2007	n/a		
IA/0051	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	25/04/2007	n/a		
IA/0050	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	25/04/2007	n/a		
N/0047	The MAH completed the list of local representatives in the PL to inlcude the two new EU Member States (Bulgaria and Romania) according to the latest	03/01/2007	n/a	PL	

	EMEA/QRD template. Furhtermore the MAH took this oportunity to chnage contact details of some local representatives. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
II/0045	Change(s) to the manufacturing process for the active substance	14/12/2006	19/12/2006		
II/0034	Change(s) to the test method(s) and/or specifications for the active substance	16/11/2006	29/11/2006		
II/0038	Change(s) to the test method(s) and/or specifications for the active substance	18/10/2006	23/10/2006		
II/0037	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	18/10/2006	23/10/2006		
II/0035	Change(s) to the test method(s) and/or specifications for the active substance	18/10/2006	23/10/2006		
II/0036	Change(s) to the test method(s) and/or specifications for the active substance	21/09/2006	27/09/2006		
IA/0044	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	25/08/2006	n/a	Annex II	

II/0031	Change(s) to the manufacturing process for the active substance	27/07/2006	07/08/2006		
IA/0043	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	28/07/2006	n/a		
IA/0042	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	28/07/2006	n/a		
IA/0041	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	28/07/2006	n/a		
II/0033	Correction of the position of the frequency of two adverse drug reactions in section 4.8 of the SPC. Update of Summary of Product Characteristics	28/06/2006	25/07/2006	SmPC	Section 4.8 of the SPC has been corrected with regard to the frequency of two adverse events: the correct frequency of "common" for "injection site reaction" and "fever" has been amended. Namely, Table 1 "Undesirable Effects in Prophylactic Clinical Studies with Premature and Bronchopulmonary Dysplasia Paediatric Populations" and Table 2 "Undesirable Effects in the Prophylactic Paediatric Congenital Heart Disease Clinical Study" in section 4.8 of the SPC have been amended to represent the adverse event of injection site reaction and fever in the correct frequency of "common", respectively. As the Package Leaflet reflects the correct frequency of "common" for injection site reaction and fever, no changes have been proposed to the PL as a result of this variation.
IA/0040	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/06/2006	n/a		
II/0032	Change(s) to the manufacturing process for the active substance	01/06/2006	08/06/2006		

N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/03/2006	n/a	PL	
IA/0028	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	12/01/2006	n/a		
IA/0027	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	12/01/2006	n/a		
IA/0026	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	12/01/2006	n/a		
IA/0025	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	12/01/2006	n/a		
N/0024	To amend the addresses of the Czech, German, Estonian, Latvian, Lithuanian and United Kingdom local representatives and the name of the local representative in Iceland. Additionally, the MAH proposes to align the labelling and the package leaflet to the current QRD template and to make some minor corrections to the Estonian, Latvian and Lithuanian translations. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2005	n/a	Labelling and PL	
II/0023	Change(s) to the manufacturing process for the active substance	16/03/2005	23/03/2005		

IA/0020	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	19/11/2004	n/a		
R/0018	Renewal of the marketing authorisation.	23/06/2004	09/09/2004	SmPC and Annex II	
II/0016	Change(s) to the test method(s) and/or specifications for the active substance	29/07/2004	04/08/2004		
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2004	n/a	PL	
II/0015	Abbott wishes to remove the statement in the current SPC that indicates that there is no data on administration of greater than 5 doses of palivizumab in a single RSV season and to include statements regarding the safety of more than 5 doses of palivizumab in a single RSV season. In line with this, amendments are proposed to the Summary of Product Characteristics, Sections 4.2 Posology and method of administration, 4.4 Special warnings and special precautions for use, 4.8 Undesirable effects and 5.1 Pharmacodynamic properties. Update of Summary of Product Characteristics	21/01/2004	25/03/2004	SmPC	
II/0013	The Marketing Authorisation Holder applied to amend the SPC for Synagis to reflect data now available following the conclusion of clinical study MI-CP048 entitled 'A Study of the Safety, Tolerance and	24/07/2003	20/10/2003	SmPC and PL	

	Efficacy of of Palivizumab (MEDI-493, Synagis) for Prophylaxis of Respiratory Syncytial Virus in Children with Congential Heart Disease'. In line with this, amendments are proposed to the Summary of Product Characteristics, Sections 4.1 Therapeutic Indications, 4.4 Special warnings and special precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 4.8 Undesirable effects, 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties. The package leaflet to be updated accordingly. This application in presented in CTD format and the revised SPC is therefore presented under Module 1 of this application. The linguistic versions of the SPC are presented under Appendix One to Module 1. Extension of Indication Update of Summary of Product Characteristics and Package Leaflet				
II/0012	Update of Summary of Product Characteristics	19/03/2003	30/06/2003	SmPC	
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/04/2003	15/05/2003	PL	
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/01/2003	03/02/2003	SmPC, Labelling and PL	

I/0010	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	17/07/2002	22/07/2002		
II/0009	Update of Summary of Product Characteristics	21/02/2002	24/05/2002	SmPC	
I/0008	20_Extension of shelf-life as foreseen at time of authorisation	21/12/2001	05/03/2002	SmPC	
II/0006	Update of or change(s) to the pharmaceutical documentation	18/10/2001	17/12/2001		
I/0007	20_Extension of shelf-life as foreseen at time of authorisation	21/06/2001	n/a	SmPC	
II/0005	Update of Summary of Product Characteristics and Package Leaflet	25/01/2001	01/06/2001	SmPC, Labelling and PL	
I/0004	24_Change in test procedure of active substance 25_Change in test procedures of the medicinal product	25/01/2001	n/a		
I/0003	12_Minor change of manufacturing process of the active substance	19/10/2000	n/a		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2000	29/09/2000	Labelling and PL	
I/0001	13_Batch size of active substance	15/03/2000	27/04/2000		