Bexsero

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/0076	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	24/04/2019	n/a		
II/0073	Update of section 4.2 of the SmPC to recommend a 3rd (booster) dose in individuals at continued risk of exposure to meningococcal disease and section 5.1 of the SmPC to add data on antibody persistence and response to a booster dose in children, adolescents	28/02/2019	28/03/2019	SmPC and PL	Please refer to Scientific Discussion 'Bexsero-H-C-002333-II-73' and to 'Bexsero-H-C-002333-P46-26'.

[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).

	and adults. This submission is based on clinical studies V72_28E1 and V72_75 and constitutes follow-on to procedure EMEA/H/C/002333/P46/026. Study V72_28E1 was a phase 3b, open label, multicentre extension study that evaluated the antibody persistence in children 4 through 12 years of age at 24 through 36 months after the last dose in follow-on subjects from the parent study V72_28. Study V72_75 was a phase 3b, open label, controlled, multicentre study that assessed the long-term antibody persistence of bactericidal activity at 4 to 7.5 years after 2-dose primary series of vaccination and the booster response to a third dose in adolescents and young adults 15 through 24 years of age who previously participated in studies V72P10 and V72_41. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1532	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation	14/03/2019	n/a		
II/0074	Update of section 4.5 of the SmPC in order to include the possibility of concomitant administration with the MenACWY vaccine based on final results from study	14/03/2019		SmPC and PL	Please refer to Scientific Discussion 'Bexsero-H-C-002333-II-74' and to

	V72_56. This was a phase 3b study assessing the safety and immunogenicity of Bexsero administered concomitantly with MenACWY vaccine as compared to their individual administration in healthy infants at approximately 3, 5, 7 and 13 months of age. This submission constitutes follow-on to procedure EMEA/H/C/002333/P46/027. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes throughout the Product Information and Annex A. The requested variation proposed amendments to the Summary of Product Characteristics, Package Leaflet and Annex A. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				'Bexsero-H-C-002333-P46-27'.
IB/0072	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	05/02/2019	n/a		
WS/1504	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Section 4.4 of the SmPC for four GSK meningococcal vaccines to include a safety warning of the risk for invasive disease caused by Neisseria meningitidis relative to individuals with familial complement deficiencies and individuals receiving	24/01/2019	28/03/2019	SmPC and PL	Based on the review of the literature reports well as the cases from the MAH's safety database, the Bexsero /Menveo SmPC has been updated to reflect that persons with familial complement deficiencies (for example, C5 or C3 deficiencies) and persons receiving treatments that inhibit terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by Neisseria meningitidis (of the group relevant for each vaccine), even if they develop antibodies following vaccination with Bexsero

	treatment that inhibits terminal complement activation (for example eculizumab). The Package Leaflets (PL) are updated accordingly. In addition, the Worksharing Applicant (WSA) took the opportunity to amend the list of local representatives in the PL of Bexsero and Menveo. Minor editorial updates in the SmPC of Bexsero and Menveo were also carried out. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(/Menveo, as applicable). The PLs have been updated accordingly.
II/0069	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	06/12/2018	n/a		
PSUSA/10043 /201801	Periodic Safety Update EU Single assessment - meningococcal group-B vaccine (rDNA, component, adsorbed)	20/09/2018	22/11/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10043/201801.
IA/0070	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	26/10/2018	n/a		
IB/0068/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	28/08/2018	n/a		

	the AS B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
IB/0067/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)	26/06/2018	n/a		
II/0059	Update of section 4.2 of the SmPC to update the dosing schedule for infants aged 3 months to 5 months and aged 2 years to 10 years based on the results from studies V72_28 and V72_28E1. Update of section 4.8 of the SmPC to include the number of subjects exposed to at least 1 dose based on the results from studies V72_28 and V72_28E1. Update of section 5.1 of the SmPC to update the information about immunogenicity in infants and children based on the results from studies V72_28 and V72_28E1. The Package leaflet is updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the product information and Annex A and also to update the list of local representatives in the package leaflet. Furthermore,	26/04/2018	07/06/2018	SmPC, Labelling and PL	Posology (two-dose primary series following by a booster) and immunogenicity in infants (3 months to 5 months): The posology for infants (age at first dose 3 months to 5 months) is two doses each of 0.5 ml for primary immunisation, the interval between primary doses is not less than 2 months. The booster is one dose between 12 and 15 months of age with an interval of at least 6 months between the primary series and booster dose. The immunogenicity after two primary doses (at 3 and a half and 5 months of age) or three primary doses (at 2 and a half, 3 and a half and 5 months of age) of Bexsero followed by a booster dose in infants starting vaccination between 2 and 5 months of age has been evaluated in an additional phase 3 clinical study. The percentages of seropositive subjects (i.e. achieving an hSBA of at least 1:4) ranged from 44% to 100% one month after the second dose and from 55% to 100% one

	Bexsero is removed from the additional monitoring list and consequently the inverted black triangle is deleted from the SmPC and package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				month after the third dose. At one month following a booster administered 6 months after the last dose, the percentages of seropositive subjects ranged from 87% to 100% for the two-dose schedule, and from 83% to 100% for the three-dose schedule. Antibody persistence was evaluated in an extension study in children 3 to 4 years of age. Comparable percentages of subjects were seropositive at 2 to 3 years after being previously vaccinated with either two doses followed by a booster of Bexsero (ranging from 35% to 91%) or three doses followed by a booster (ranging from 36% to 84%). In the same study the response to an additional dose administered 2 to 3 years after the booster was indicative of immunological memory as shown by a robust antibody response against all Bexsero antigens, ranging from 81% to 100% and from 70% to 99%, respectively. These observations are consistent with adequate priming in infancy with both a two-dose and a three-dose primary series followed by a booster of Bexsero. Posology and immunogenicity in children (2 years to 10 years): The interval between primary doses for children (2 years to 10 years) is decreased to 1 month. The immunogenicity after two doses of Bexsero administered either one or two months apart in children 2 to 10 years of age has been evaluated in two phase 3 clinical studies. In the first study, participants received two doses of Bexsero two months apart. The seroresponse rates and hSBA GMTs were high after the two-dose schedule in children against each of the vaccine antigens. High percentages of subjects were seropositive in the second

					study, in which two doses of Bexsero were administered one month apart. An early immune response after the first dose was also evaluated. The percentages of seropositive subjects (i.e. achieving an hSBA of at least 1:4) across strains ranged from 46% to 95% at one month after the first dose and from 69% to 100% at one month after the second dose.
IB/0066	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	24/04/2018	n/a		
IB/0064/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.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	13/03/2018	n/a		
IB/0063/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.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.b - Change in the specification parameters	21/12/2017	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
IB/0062/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) 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	05/12/2017	n/a		
IB/0061/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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	27/10/2017	n/a		

R/0053	Renewal of the marketing authorisation.	20/07/2017	18/09/2017	Labelling	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Bexsero in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10043 /201701	Periodic Safety Update EU Single assessment - meningococcal group-B vaccine (rDNA, component, adsorbed)	01/09/2017	n/a		PRAC Recommendation - maintenance
IB/0060	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)	31/08/2017	n/a		
IB/0057	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	26/07/2017	n/a		
IB/0058/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.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	17/07/2017	n/a		
II/0054	Update of section 4.8 of the SmPC in order to add the adverse reactions “injection site reactions (including	06/07/2017	18/09/2017	SmPC, Labelling and	Based on post marketing surveillance findings following vaccination with Bexsero, the product information of Bexsero

	extensive swelling of the vaccinated limb)" and "injection site nodule which may persist for more than one month" with a frequency not known. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			PL	(section 4.8 of the SmPC and package leaflet) is updated to include, across all age groups from infants to adults, the adverse reactions "injection site reactions (including extensive swelling of the vaccinated limb" and "injection site nodule which may persist for more than one month)" with a frequency not known.
IB/0056/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	21/06/2017	n/a		
IB/0055/G	This was an application for a group of variations. B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR B.I.b.1.z - Change in the specification parameters	21/06/2017	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Other variation				
II/0051	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	18/05/2017	n/a		
II/0048	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	23/03/2017	n/a		
IB/0050	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	06/03/2017	n/a		
IB/0049	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	08/02/2017	18/09/2017	SmPC	
IA/0047/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.b.2.a - Change in test procedure for AS or starting	03/11/2016	n/a		

	material/reagent/intermediate - Minor changes to an approved test procedure B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol 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				
II/0046	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	15/09/2016	n/a		
II/0045	Update of section 4.5 "Interaction with other medicinal products and other forms of interaction" of the SmPC, to include information on the concomitant vaccination of Bexsero with the meningococcal group C-CRM conjugate vaccine. The Package Leaflet is updated accordingly. The MAH took the opportunity of this variation to update the contact details in the PL. Furthermore, the PI is brought in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	18/09/2017	SmPC, Annex II, Labelling and PL	Results of a study, to evaluate the safety, tolerability and immunogenicity of Bexsero when administered alone or concomitantly with meningococcal group C-CRM conjugate vaccine to healthy infants according to different immunization schedules and to healthy children aged 2 through 10 years, show that Bexsero can be given concomitantly with the meningococcal group C-CRM conjugate vaccine.
II/0044/G	This was an application for a group of variations. Group of 2 type II variations. The first variation	15/09/2016	18/09/2017	SmPC and PL	Update of section 4.8 of the SmPC to include fever as adverse reaction in adolescents from 11 years of age and adults, and to add hypotonic-hyporesponsive episode (HHE) as adverse

	concerns the update of section 4.8 of the SmPC to include fever as adverse reaction in adolescents from 11 years of age and adults, and to include hypotonic-hyporesponsive episode (HHE) as adverse reaction in infants and children up to 10 years of age. The PL is updated accordingly. Additionally, section 2 of the PL is updated to reflect the apnoea class labelling statement in the SmPC. The second variation concerns the update of sections 4.4 and 5.1 of the SmPC to reflect safety and immunogenicity data from a clinical study involving the use of Bexsero in subjects 2 through 17 years of age with increased risk of meningococcal disease. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				reaction in infants and children up to 10 years of age. The frequency of these adverse reactions is not known. Update of sections 4.4 and 5.1 of the SmPC to reflect the results of the phase 3 clinical study, in children and adolescents with complement deficiencies, asplenia, or splenic dysfunction (the study shows an immune response in immunocompromised subjects) and to add a warning to individuals with impaired immune responsiveness, that they may have reduced antibody response to active immunization.
PSUSA/10043 /201601	Periodic Safety Update EU Single assessment - meningococcal group-B vaccine (rDNA, component, adsorbed)	02/09/2016	n/a		PRAC Recommendation - maintenance
II/0043/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical	21/07/2016	n/a		

	forms manufactured by complex manufacturing processes B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product or a new bioequivalence study				
IA/0042/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	08/04/2016	n/a		
IB/0040	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	13/01/2016	n/a		
IB/0039/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.4.b - Change to in-process tests or limits applied	12/01/2016	n/a		

	during the manufacture of the AS - Addition of a new in-process test and limits				
IG/0639	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	09/12/2015	n/a		
II/0033	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	19/11/2015	n/a		
II/0032/G	This was an application for a group of variations. C.I.4 Update of section 5.1 of the SmPC to add information regarding the waning of antibody titers based on data from study V72P12E2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	28/01/2016	SmPC	
II/0036	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	22/10/2015	n/a		

IAIN/0037/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH 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.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.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release 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)	24/09/2015	28/01/2016	SmPC, Annex II, Labelling and PL	
PSUSA/10043 /201501	Periodic Safety Update EU Single assessment - meningococcal group-B vaccine (rDNA, component, adsorbed)	10/09/2015	n/a		PRAC Recommendation - maintenance
IB/0034/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the	07/09/2015	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IAIN/0035/G	This was an application for a group of variations. B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR	11/08/2015	n/a		
II/0031	Update of section 4.8 of the SmPC in order to amend the safety information on arthralgia and headache as very common solicited systemic adverse event (AEs) under children 2 through 10 years of age. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct some typo errors. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	28/01/2016	SmPC and PL	This procedure amend section 4.8 of the Bexsero SmPC to include “headache” among the very common Adverse Events (AEs) listed in the system organ class (SOC) “Nervous and system disorders” and “arthralgia” among the very common AE listed in the SOC “Muscoloskeletal and connective tissue disorders”.

IB/0030	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	12/05/2015	n/a		
IA/0029	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)	24/04/2015	n/a		
IA/0027	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	27/03/2015	n/a		
IB/0026	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	16/03/2015	n/a		
II/0025	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	26/02/2015	n/a		
PSUSA/10043 /201407	Periodic Safety Update EU Single assessment - meningococcal group-B vaccine (rDNA, component, adsorbed)	12/02/2015	n/a		PRAC Recommendation - maintenance
II/0024	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information from post marketing experience regarding allergic reactions (including anaphylactic reactions), syncope or vasovagal	22/01/2015	28/01/2016	SmPC and PL	Introduction in the SmPC of information regarding the safety profile of Bexsero in terms of allergic reactions (including anaphylactic reactions), syncope or vasovagal responses to injection have been done after analysis of post marketing

	responses to injection. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to clarify information already reported in sections 4.4, 4.8 and 6.6 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				data. Other minor clarifications of already reported safety information have been also performed by the MAH. The Package leaflet has been updated accordingly.
IB/0022	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	12/12/2014	n/a		
PSUV/0019	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IB/0021/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.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	10/09/2014	n/a		
II/0020	Change in the manufacturing porcess 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	24/07/2014	n/a		Change in the manufacturing porcess of the active substance

	product and is not related to a protocol				
IB/0018	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	10/07/2014	n/a		
II/0014	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	26/06/2014	n/a		
II/0013	Update of SmPC section 5.1 with information on persistence of the immune response in adolescents, based on results of study V72P10E1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	01/10/2014	SmPC	Study V72P10E1 was designed to provide information on antibody persistence following vaccination in adolescents with Bexsero. The immunogenicity results, are considered as expected, i.e. following a peak response at 1 month following vaccination the antibody levels decline but remain elevated compared to baseline and the control group levels. No relevant safety data was collected in the study as this study only consisted of a blood draw. The data from study V72P10E1 support a positive benefit-risk balance for Bexsero.
II/0012	Update of section 4.2 of the SmPC in order to revise the recommendations on administration of the booster dose during the second year of life, as requested by the CHMP in the outcome of the assessment of a post-authorisation measure. The PL is being updated accordingly. In addition, the list of local representatives in the PL has also been updated.	26/06/2014	01/10/2014	SmPC and PL	Result of the studies in infants, testing different dose regimens, indicate a waning in levels of circulating antibodies during the second year of life in subjects who received their first priming dose within the first six months of life, especially when the 2, 3, 4 month priming schedule is used. The data provided indicate that there are no significant changes if the booster dose is given between 12 and 15 months and this

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				allows some flexibility in the vaccination schedule. Based on the results of these studies, the CHMP recommends for infants receiving their first priming dose within the first six months of life to give the booster dose as early as possible, between 12 and 15 months, and to include a note informing that the booster dose should not be given later than 24 months.
IB/0017	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/05/2014	n/a		
IB/0016	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	06/05/2014	n/a		
II/0008	Submission of final study report for a phase III study to evaluate the effect of Menveo and Bexsero on pharyngeal carriage of N. meningitidis in young adults (study V72_29). This study has been conducted as a post-authorisation measure required in the Risk Management Plan. Section 4.8 of the SmPC is updated with information on the increased safety database. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/04/2014	01/10/2014	SmPC	The MAH provided results from a phase-3, multicentre, observer-blind randomized trial that enrolled university students of 18 to 24 years of age in the UK and investigated the effect of Menveo and Bexsero on pharyngeal carriage of N. meningitidis. While in this study the primary objectives were not achieved and the overall impact on carriage was small, it is agreed that even a small reduction on carriage could contribute to herd immunity, though demonstration of that would require further data. Based on experience with other bacterial vaccines the CHMP concluded that it is likely that very high levels of antibodies are needed to protect against mucosal colonisation, compared to levels needed to protect against invasive disease. Therefore, the CHMP concluded that the current results do not negatively influence the benefit risk balance of Bexsero.

IG/0426	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	11/04/2014	n/a		
PSUV/0010	Periodic Safety Update	06/02/2014	n/a		PRAC Recommendation - maintenance
IB/0009/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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/12/2013	n/a		
IA/0011	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	18/11/2013	n/a		
II/0005	Update of the safety information in SmPC section 4.8 following integration of results from several new studies into the safety database, as requested by the CHMP. In particular, the frequency of rash has been differentiated by age groups, the frequency of urticaria has been updated and the information on the risk of fever has been expanded. The PL has been updated in accordance. In addition, the SmPC, Annex II, Labelling and PL have been aligned with the latest QRD template version 9.0, list of local representatives in the PL has been updated, and the Labelling has been corrected to properly reflect all approved	24/10/2013	01/10/2014	SmPC, Annex II, Labelling and PL	The MAH provided updated integrated safety analysis that included data from 7802 patients. Based on this data, the MAH proposed to update frequency information for adverse events of rash and urticaria, which was accepted by the CHMP. In addition, the CHMP requested to include more detailed description of the increased risk of fever if Bexsero is administered together with routine vaccines (69% to 79% of subjects experienced fever ≥ 38°C when Bexsero was co administered with routine vaccines compared with 44% to 59% of subjects receiving the routine vaccines alone).

	presentations. Minor corrections are made also in Annex A. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IB/0007	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	10/10/2013	n/a		
IB/0006	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	31/07/2013	n/a		
IB/0004	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	01/07/2013	n/a		
IB/0002	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/05/2013	n/a		
IB/0003	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	30/04/2013	n/a		
IAIN/0001/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	10/04/2013	n/a		

	system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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				