Zostavax

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
IA/0142/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	30/06/2022		Annex II 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).

	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)				
IG/1506	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)	31/05/2022	n/a		
T/0140	Transfer of Marketing Authorisation	14/03/2022	01/04/2022	SmPC, Labelling and PL	
N/0139	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/12/2021	01/04/2022	PL	
II/0138	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	28/10/2021	n/a		
IB/0136	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	18/08/2021	n/a		
IB/0137	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	20/07/2021	n/a		

IA/0135/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer 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	07/06/2021	n/a		
II/0132	Submission of the final study report from the post-licensure observational study of the long-term effectiveness of Zostavax (Protocol 024) listed as category 3 study in the RMP. Consequently, section 5.1 of the SmPC was updated. With this application, the post authorisation measure REC 23 is fulfilled. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and include editorial corrections in annex A. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	03/06/2021	18/08/2021	SmPC and PL	SmPC new text: 5. PHARMACOLOGICAL PROPERTIES 5.1 Pharmacodynamic properties […] Long-term effectiveness study in individuals 50 years of age or older In a large-scale US prospective observational cohort study of the long-term effectiveness of ZOSTAVAX, individuals 50 years of age or older at the time of vaccination were followed for the occurrence of HZ and PHN using validated endpoints. Out of 1,505,647 study individuals, 507,444 received ZOSTAVAX between 2007 and 2018. A total of 75,135 confirmed HZ cases and 4,954 confirmed PHN cases (> 90 days of zoster-associated pain) were observed. The results

					showed that ZOSTAVAX is effective in reducing HZ and PHN incidence for over 8-10 years in vaccinated individuals as compared to an unvaccinated reference group. Estimates of vaccine effectiveness (VE) against HZ by age at vaccination and average VE estimates over the first 3, 5, 8 and 10 years postvaccination are shown below (see Table 6). […] Estimates of VE against PHN by age at vaccination and average VE estimates over the first 3, 5 and 8 years postvaccination are shown below (see Table 7). […] For more information, please refer to the Summary of Product Characteristics.
IB/0134	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	26/05/2021	n/a		
IG/1375	A.7 - Administrative change - Deletion of manufacturing sites	25/03/2021	n/a		
IA/0131/G	This was an application for a group of variations. B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	27/11/2020	18/08/2021	SmPC, Labelling and PL	

IB/0129	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/08/2020	18/08/2021	SmPC, Annex II, Labelling and PL	
IA/0130	A.7 - Administrative change - Deletion of manufacturing sites	15/07/2020	n/a		
IG/1191/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer 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	06/03/2020	n/a		
N/0127	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/01/2020	18/08/2021	PL	
WS/1740	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	23/01/2020	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				
PSUSA/9289/ 201905	Periodic Safety Update EU Single assessment - shingles (herpes zoster) vaccine (live)	28/11/2019	n/a		PRAC Recommendation - maintenance
WS/1512	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.z - Change in container closure system of the Finished Product - Other variation	17/01/2019	n/a		
PSUSA/9289/ 201805	Periodic Safety Update EU Single assessment - shingles (herpes zoster) vaccine (live)	29/11/2018	n/a		PRAC Recommendation - maintenance
II/0117	Update of sections 4.5 and 5.1 of the SmPC to update the information about concomitant use of Zostavax with a 23-valent pneumococcal polysaccharide vaccine. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	29/11/2018	24/10/2019	SmPC and PL	In a US effectiveness cohort study of 35,025 adults ≥ 60 years old, no increased risk of herpes zoster was observed in individuals who received Zostavax and 23-valent pneumococcal polysaccharide vaccine concomitantly (n=16,532) as compared to individuals receiving Zostavax one month to one year after 23-valent pneumococcal polysaccharide vaccine (n=18,493) in routine practice. The adjusted hazard ratio comparing the incidence rate of HZ in the two groups was 1.04 (95% CI, 0.92, 1.16) over a median follow-up of 4.7 years. The data do not indicate that concomitant administration alters the effectiveness of

					Zostavax.
IA/0124	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	21/11/2018	n/a		
IG/0977	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	19/10/2018	n/a		
IG/0973	A.7 - Administrative change - Deletion of manufacturing sites	21/09/2018	n/a		
IAIN/0119	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	20/08/2018	n/a		
PSUSA/9289/ 201705	Periodic Safety Update EU Single assessment - shingles (herpes zoster) vaccine (live)	30/11/2017	n/a		PRAC Recommendation - maintenance
II/0115	Update section 4.4 of the SmPC to complement the safety information regarding the vaccination of contraindicated immunodeficient individuals based on three post-marketing reports. In addition, the MAH took the opportunity to make some editorial changes to the English product information and to following linguistic versions of the product information: Dutch, Czech, Greek, Spanish, Italian, Norwegian, Polish, Portuguese, Swedish, Slovenian, Slovak, Croatian, Hungarian and Finish. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	23/11/2017	15/01/2018	SmPC and PL	ZOSTAVAX is a live, attenuated varicella-zoster vaccine and administration to individuals who are immunosuppressed or immunodeficient may result in disseminated varicella-zoster virus disease, including fatal outcomes.

	data				
WS/1199/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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	16/11/2017	n/a		
IG/0856/G	This was an application for a group of variations. 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.f.1.e - Stability of FP - Change to an approved stability protocol	10/11/2017	n/a		
II/0112	Update of section 5.1 of the SmPC in order to add information on long-term effectiveness of Zostavax on herpes zoster and postherpetic neuralgia in	15/06/2017	15/01/2018	SmPC and Labelling	In a large-scale ongoing US prospective observational cohort study of the long-term effectiveness of ZOSTAVAX, individuals 50 years of age or older at the time of

	individuals 50 years of age or older following the first interim results from the post-licensure observational study (Protocol 024) listed as category 3 study in the RMP. In addition, the marketing authorisation holder took the opportunity to bring the product information 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				vaccination are being followed for the occurrence of herpes zoster (HZ) and post-herpetic neuralgia (PHN) using validated endpoints. In an interim analysis of the 2007 to 2014 study period, out of 1,355,720 study individuals, 392,677 received ZOSTAVAX. A total of 48,889 confirmed HZ cases and 3,316 confirmed PHN cases (>90 days of zoster-associated pain) were observed. The results showed that ZOSTAVAX is effective in reducing HZ and PHN incidence in vaccinated individuals as compared to an unvaccinated reference group. Vaccine effectiveness (VE) against HZ was evaluated for up to eight years postvaccination. VE estimates by age at vaccination and average VE estimates over the first 3 and 5 years postvaccination can be found in section 5.1 of the product information.
N/0111	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/03/2017	15/01/2018	PL	
II/0109/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 forms manufactured by complex manufacturing processes B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	23/03/2017	n/a		

	control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method				
IG/0777	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2017	15/01/2018	SmPC, Labelling and PL	
IG/0758	A.1 - Administrative change - Change in the name and/or address of the MAH	11/01/2017	15/01/2018	SmPC, Labelling and PL	
N/0107	Update of the package leaflet with revised contact details of the local representatives. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2016	15/01/2018	PL	
PSUSA/9289/ 201605	Periodic Safety Update EU Single assessment - shingles (herpes zoster) vaccine (live)	01/12/2016	n/a		PRAC Recommendation - maintenance
WS/0983	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	06/10/2016	n/a		
WS/0947	This was an application for a variation following a	28/07/2016	n/a		

	worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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				
WS/0739	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	21/07/2016	n/a		
IA/0104	A.7 - Administrative change - Deletion of manufacturing sites	14/07/2016	n/a		
IAIN/0103	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	08/07/2016	n/a		
IG/0696	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	20/06/2016	n/a		

IG/0695	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/06/2016	n/a		
IG/0687	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	30/05/2016	n/a		
R/0096	Renewal of the marketing authorisation.	17/12/2015	11/02/2016	SmPC and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Zostavax continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
X/0085	Annex I_2.(e) Change or addition of a new route of administration	22/10/2015	18/12/2015	SmPC, Labelling and PL	For further information please refer to: "Zostavax-H-C-674-AR-X-85".
PSUSA/9289/ 201505	Periodic Safety Update EU Single assessment - shingles (herpes zoster) vaccine (live)	03/12/2015	n/a		PRAC Recommendation - maintenance
IG/0625	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/11/2015	n/a		
WS/0786	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	17/09/2015	n/a		

	B.II.c.z - Change in control of excipients in the Finished Product - Other variation				
PSUSA/9289/ 201411	Periodic Safety Update EU Single assessment - shingles (herpes zoster) vaccine (live)	11/06/2015	n/a		PRAC Recommendation - maintenance
N/0093	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/06/2015	18/12/2015	PL	
WS/0718	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	21/05/2015	n/a		
WS/0706	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	21/05/2015	n/a		
II/0090	Update of sections 4.2, 4.8 and 5.1 of the SmPC to include information on the safety and immunogenicity of a booster dose of Zostavax	23/04/2015	18/12/2015	SmPC	The Summary of Product Characteristics has been updated to reflect the following: - Section 4.2: The need for booster doses remains

	further to additional results from study P029. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				unknown. - Section 4.8: In a placebo-controlled, double-blind, study, 98 adults 60 years of age or older received a second dose of ZOSTAVAX 42 days following the initial dose; the vaccine was generally well tolerated. The frequency of vaccine-related adverse experiences after the second dose of ZOSTAVAX was generally similar to that seen with the first dose. In an open-label study, ZOSTAVAX was administered as a booster dose to 201 HZ history-negative subjects 70 years of age or older who had received a first dose approximately 10 years previously, and as a first dose to 199 HZ history-negative subjects 70 years of age or older. The vaccine was generally well tolerated; the frequency of vaccine-related adverse experiences after the booster dose of ZOSTAVAX was generally similar to that seen with the first dose. - Section 5.1: Immunogenicity in Subjects Receiving a Booster Dose In an open-label study, ZOSTAVAX was administered as: (1) a booster dose to 201 HZ history-negative subjects 70 years of age or older who had received a first dose approximately 10 years previously as participants in the SPS, and (2) a first dose to 199 HZ history-negative subjects 70 years of age or older. The antibody response to vaccine 6 weeks postvaccination as measured by gpELISA was comparable in the booster dose and first dose group (GMT of 389.1 vs 368.8 gpELISA units/mL, respectively). The geometric mean fold-rise of the VZV antibody response, as measured by gpELISA, from prevaccination to Week 6 postvaccination was 1.5 (95% CI: [1.4 to 1.6]) in

					both groups.
WS/0715	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.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	23/04/2015	n/a		
WS/0693/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	23/04/2015	n/a		
WS/0664/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	26/03/2015	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0084	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	26/03/2015	n/a		
WS/0626	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	18/12/2014	n/a		
IG/0511	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	08/12/2014	n/a		
PSUV/0078	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance

WS/0644	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change to in-process tests or limits applied during the manufacture of the active substance 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	20/11/2014	n/a		
II/0077	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	12/01/2015	SmPC	
IG/0493	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	21/10/2014	n/a		
II/0073	Update of section 4.8 of the SmPC in order to add "herpes zoster (vaccine strain)" as post-marketing adverse event. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to revise section 4.8 of the SmPC to update the figure of the patient vaccinated with Zostavax in clinical trials and to harmonize the term "herpes zoster-like rash" for consistency in this section; revise the wording of the reconstitution	25/09/2014	12/01/2015	SmPC, Annex II and PL	Following post marketing report, herpes zoster (vaccine strain) was added to the product information for Zostavax. Indeed, on a random basis, the vaccine strain may be re-activated in vaccinees and may cause a Zoster exacerbation. At present, the frequency of vaccine strain related zoster is unknown.

	instructions for the Health Care professionals in section 6.6 of the SmPC and the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0079	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/08/2014	n/a		
WS/0479	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. to add a site responsible for performing release testing of varicella drug substance B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	24/07/2014	n/a		
WS/0548/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	26/06/2014	n/a		

	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)				
PSUV/0069	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance
IG/0435	A.1 - Administrative change - Change in the name and/or address of the MAH	06/05/2014	12/01/2015	SmPC, Labelling and PL	
IG/0436	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	30/04/2014	n/a		
IG/0429	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)	16/04/2014	n/a		
IG/0434	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	09/04/2014	n/a		
WS/0453	This was an application for a variation following a worksharing procedure according to Article 20 of	18/12/2013	n/a		

	Commission Regulation (EC) No 1234/2008. addition to a new in-process test during manufacture of varicella drug substance 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				
II/0065/G	This was an application for a group of variations. Additional manufacturing facility for varicella drug substance and addition of a new in-process test and limit applied during the manufacture of varicella drug 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.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	18/12/2013	12/01/2015	Annex II and PL	
WS/0418/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. minor change to test procedure for active substance	24/10/2013	n/a		

	and finished product 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)				
WS/0404/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of analytical methods in order to align with compendial procedures and guidances B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting 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	25/07/2013	n/a		
IG/0312	C.I.z - Changes (Safety/Efficacy) of Human and	13/06/2013	n/a		

	Veterinary Medicinal Products - Other variation				
WS/0363	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes 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 medicinal product and is not related to a protocol	25/04/2013	n/a		
WS/0349	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. change in the test procedure of the active substance 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	25/04/2013	n/a		
A20/0052	Art 20 review: Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 March 2012, the opinion of the CHMP further to	13/12/2012	13/02/2013	SmPC, Annex II and PL	Please refer to the Assessment Report: Zostavax-H-674-A20-52-Assessment Report-Article 20

	the evaluation of the most recent published data and post marketing surveillance regarding the vaccination with measles, mumps, rubella and varicella vaccines in pregnant women and immunocompromised subjects. The CHMP was requested to assess the impact thereof on the risk-benefit balance of Zostavax in these specific populations and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawnwithdrawn.				
IG/0261/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	30/01/2013	n/a		
II/0058	to introduce a second PSF skid for the manufacture of varicella vaccine bulk 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	13/12/2012	n/a		

II/0054	change in the specification of the varicella clarified bulk B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	20/09/2012	20/09/2012		
II/0055	The MAH proposed the update of section 5.1 of the SmPC to add data on the Short-Term Protection Study (STPS - P004-05) and on the Long-Term Protection Study (LTPS - P013). The Package Leaflet and Labelling were proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet (Cyprus and Malta). Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	23/08/2012	SmPC, Annex II, Labelling and PL	Within this procedure, the final CSR of the long-term persistence study (LTPS) was assessed, which fulfils Follow-Up Measure (FUM) 006. Prior to this LTPS, there was an interim efficacy report produced (on December 21st, 2007), which related to the short-term persistence study (STPS), which was previously assessed within the framework of FUM 006. This variation aims to reflect the final study results of the above studies in section 5.1 of the SmPC. This final report is consistent with previous STPS results and previous interim reports of LTPS, pointing to a gradual decrease in vaccine efficacy. Using key efficacy analysis in LTPS population where age and calendar time were adjusted, Vaccine Efficacy (VE) on Herpes zoster (HZ) was found to decrease over time, from 51.3% in the original shingles protection study (SPS), through 39.6% in STPS and 21.1% in the LTPS (12 years after randomization). Similar trends were observed for VE HZ Burden of Illness (BOI) and VE post-herpetic neuralgia (PHN) endpoints.
IB/0057	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	12/07/2012	n/a		

WS/0259	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in batch size of intermediate B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	21/06/2012	21/06/2012		
II/0046	Update of sections 4.8 and 5.1 of the SmPC to include data on vaccine efficacy and safety in adults aged 50 to 59 years based on a Clinical Trial to Evaluate the Efficacy, Immunogenicity, Safety and Tolerability of ZOSTAVAX in Subjects 50 to 59 Years of Age (FUM 036), which has previously been assessed by the CHMP. The PL is updated accordingly. 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	16/02/2012	21/03/2012	SmPC and PL	Study P022 evaluated the efficacy, immunogenicity and safety of Zostavax in subjects 50 to 59 years old. The efficacy data from this study demonstrated that based on a sample size of 129 cases a vaccine efficacy for Herpes Zoster (VEHZ) of 69.8% was achieved in the intent-to-treat (ITT) population over a 1.3 year follow-up. According to the initial sample size calculation the trial should be continued until 96 evaluable cases of HZ were observed. The extended number of events was due to on-going operational activities of suspected HZ cases following confirmation of the planned 96 HZ cases. Vaccine efficacy based on the first 96 HZ cases was comparable with the VE calculated on the 129 HZ cases accrued in the study. VEHZ calculated on the basis of the first 96 HZ cases was 70.3 % (95% CI: [54.7%, 82.4%]). In comparison based on 129 HZ cases accrued the overall estimated VEHZ was 69.8% (95% CI: [54.1%, 80.6%]). The immunogenicity data showed that only 49.8% of Zostavax recipients had at least a 2-fold increase in antibody titres. No information on the cellular immune

					response is available. It is thought that both humoral and cellular immunity are crucial to control reactivation of VZV however it is still unknown which antibody titres or CMI responses are predictive for long term protection. In view of safety, the CHMP considered that overall the findings from this study are consistent with the known safety profile of Zostavax. As anticipated, a slightly higher reactogenicity has been found in subjects 50 to 59 years old compared to subjects ≥ 60 years of age. The Product Information was updated to reflect these study results.
WS/0225	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in batch size (including batch size ranges) of active substance or intermediate B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	15/03/2012	15/03/2012		
IG/0159	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	09/03/2012	n/a		
IG/0156	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	24/02/2012	n/a		

II/0045	To update sections 4.3, 4.8 and 5.1 of the SmPC to include the safety and immunogenicity data in subjects under corticosteroid therapy based on the CHMP assessment of a clinical study in patients receiving corticosteroid therapy (P017). In addition, the MAH took the opportunity to update section 9 of the SmPC to add the date of the renewal in the SmPC, to make minor editorial changes to Annex II , and to update section 16 "INFORMATION IN BRAILLE" of the Labelling in line with current guidance. 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	19/01/2012	21/02/2012	SmPC, Annex II and Labelling	In a double-blind, placebo-controlled, randomized clinical trial, Zostavax was administered to 206 subjects 60 years of age or older who were receiving chronic/maintenance systemic corticosteroid therapy at a daily dose equivalent of 5 to 20 mg of prednisone for at least 2 weeks prior to enrolment, and 6 weeks or more following vaccination to assess the immunogenicity and safety profile of Zostavax. In view of immunogenicity, compared with placebo, Zostavax induced a higher varicella zoster virus (VZV-) specific gpELISA antibody geometric mean titre (GMT) at 6 weeks postvaccination (GMT of 531.1 vs. 224.3 gpELISA units/ml, respectively). The Geometric mean fold-rise of immune response following vaccination as measured by gpELISA was 2.3-fold (95% CI: [2.0 to 2.7]) compared to 1.1-fold (95% CI: [1.0 to 1.2]) in the placebo group. The safety profile seen in this study was generally comparable to that seen in previous studies.
II/0037	Update of section 4.8 of the SmPC in order to include the term "nausea" based on post-marketing experience. The Package Leaflet was updated in accordance. The MAH also took the opportunity to clarify the table of adverse events in section 4.8 to include that "varicella" has been observed as an adverse event in line with existing text in sections 4.4 and 4.8 of the SmPC. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.	15/12/2011	20/01/2012	SmPC and PL	Review of post marketing reports suggests a temporal relation between vaccination with Zostavax and the onset of nausea shortly after vaccination. The addition of the adverse reaction nausea to the product information was therefore considered justified. Moreover the Product Information was revised to provide more concise information in section 4.8 of the SmPC on the very rare adverse reaction 'varicella' caused by the vaccine virus in line with existing wording in section 4.4 of the SmPC. The Package Leaflet was 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				
IB/0047	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	05/01/2012	n/a		
IG/0093	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	12/08/2011	n/a		
IG/0085	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)	08/07/2011	n/a		
IB/0036	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	29/04/2011	n/a		
IG/0059/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	15/04/2011	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
R/0034	Renewal of the marketing authorisation.	20/01/2011	24/03/2011	Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of ZOSTAVAX remains positive, but considers that its safety profile is to be closely monitored for the following reasons: Since approval of ZOSTAVAX in 2006, several adverse drug reactions (ADRs) have been added to the reference safety information, however the post-authorisation safety data regarding the use of ZOSTAVAX within the EU are limited and it cannot be excluded that additional ADRs may be detected. The CHMP decided that the MAH should continue to submit 6-monthly PSURs. Therefore, based upon the safety profile of ZOSTAVAX, which requires the submission of 6-monthly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
WS/0099/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To change the manufacturer of a reagent. To update certificates of suitability. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The	17/02/2011	17/02/2011		

	change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer				
IB/0035/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	27/01/2011	n/a		
II/0032	Update of the section 4.4 of the SmPC based upon a safety report about a secondary transmission of Oka vaccine strain varicella zoster virus (VZV) from a vaccinee who did not develop a rash post vaccination with varicella virus vaccine live (Oka/Merck) to a healthy non-vaccinee. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC	Following a post-marketing report on a case of possible secondary transmission of the OKA strain related to vaccination with Varivax, the MAH proposed to update the SmPC subsection on transmission. Zostavax and Varivax both contain the attenuated varicella virus strain OKA/Merck. Although there is currently no report of secondary transmission of this vaccine strain following administration of Zostavax a theoretical risk remains. Therefore the CHMP endorsed the proposed update of Zostavax SmPC section 4.4 to reflect the possibility of secondary transmission following vaccination.

WS/0044	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To implement a change in the immediate packaging of the finished product. B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products	23/09/2010	25/10/2010	SmPC and PL	
IB/0033	Change on the test procedure of a reagent. B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	07/10/2010	n/a		
II/0031	B.I.a.2.c. Changes in the manufacturing process of the active substance. The change refers to a biological / immunological substance or use of a different chemically derived 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	23/09/2010	29/09/2010		

WS/0017/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2 Changes in the manufacturing process of the active substance c) The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol. B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance a) Tightening of specification limits for medicinal products subject to Official Batch Release 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.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 Official Batch Release	23/09/2010	23/09/2010		
WS/0018	This was an application for a variation following a	22/07/2010	22/07/2010		

	worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e) Change in the test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance. Other changes to a test procedure (including replacement or addition) of the active substance 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				
IA/0030	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	29/04/2010	n/a		
IA/0029/G	This was an application for a group of variations. To change in the name of the Drug substance and drug product manufacturer. Following the merger between Merck & Co., Inc. and Schering-Plough Corporation, the name of the company has changed from Merck & Co., Inc. to Merck Sharp & Dohme Corp. A.4 - Administrative change - Change in the name	30/03/2010	n/a	Annex II	

	and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)				
II/0028	To scale-up the number of production roller bottles planted during the manufacture of Varicella Harvested Virus Fluid process. Update of or change(s) to the pharmaceutical documentation	18/02/2010	02/03/2010		
II/0027	Update of the detailed description of pharmacovigilance system (DDPS) including the change of the Qualified Person Responsible for Pharmacovigilance (QPPV). The version number of the DDPS in Annex II has been updated accordingly. The MAH also took the opportunity to update the version number of the Risk Management Plan in Annex II. Changes to QPPV Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II	The DDPS has been updated to version 2.0 in order to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.
II/0026	include arthralgia, myalgia, injection-site urticaria and injection-site rash in section 4.8 of the SPC based on an analysis of the MAH's safety database. The PL is updated accordingly.	24/09/2009	28/10/2009	SmPC and PL	Following the review of safety reports received during post-marketing surveillance and entered into the MAH's safety database the MAH submitted this variation to update section 4.8 of the SPC on post-marketing experience to

	Update of Summary of Product Characteristics and Package Leaflet				include the adverse reactions injection-site rash, injection-site urticaria, arthralgia and myalgia.
II/0025	Change(s) to the test method(s) and/or specifications for the finished product	24/09/2009	01/10/2009		
IA/0024	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	08/07/2009	n/a		
IA/0023	IA_03_Change in the name of the active substance	30/06/2009	n/a	SmPC, Labelling and PL	
IA/0022	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	09/06/2009	n/a		
II/0018	To update sections 4.5 and 5.1 of the SPC to include information on the safety and immunogenicity of the concomitant administration of Zostavax and 23-valent pneumococcal polysaccharide vaccine based on a placebo-controlled, double-blind clinical study on the safety, tolerability, and immunogenicity of Zostavax when administered concomitantly with Pneumovax 23 in subjects 60 years of age or older. The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	23/04/2009	29/05/2009	SmPC and PL	A clinical study on the safety, tolerability, and immunogenicity of Zostavax when administered concomitantly with Pneumovax 23 in subjects 60 years of age or older showed that the level of Varicella zoster virus (VZV) antibody response in subjects who received Zostavax concomitantly with Pneumovax 23 was inferior, to the VZV antibody response in subjects who received the vaccines nonconcomitantly. Levels of VZV antibody response in the concomitant group were consistent with levels seen in previous studies of Zostavax, but did not meet the noninferiority criterion pre-specified in this study. Although the geometric mean fold rise (GMFR) of the VZV antibody response in the concomitant group was acceptable, the GMFR was noticeably lower than in the non-concomitant group (1.9 vs. 3.1). Concomitant administration did not

					affect the antibody response to the Pneumovax serotypes tested. In order to avoid a potential decrease in Zostavax immunogenicity, Zostavax and Pneumovax should not be given concomitantly. The Product Information was amended to reflect this information.
II/0017	To add the adverse event lymphadenopathy to section 4.8 of the Summary of Product Characteristics (SPC) based on a review of postmarketing reports. The Package Leaflet (PL) is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	23/04/2009	29/05/2009	SmPC and PL	From the time of the Marketing Authorisation up until 4 September 2008 there have been a total of 10 postmarketing reports from healthcare providers identified for zoster vaccine live (Oka/Merck) in the MAH's adverse event database with the preferred term "lymphadenopathy". Of those reports, 6 were identified to be temporally related to vaccination with the vaccine. The average time of onset from vaccination to detection of lymphadenopathy was 3 days with a range of 2 to 6 days. . The average time of onset supports the acuity of this event. The term "lymphadenopathy' was therefore included in the SPC under the MedDRA SOC "Blood and lymphatic disorders with the frequency category "unknown" as no frequency could be determined based on clinical studies.
IB/0021	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	29/05/2009	n/a		
IA/0020	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	25/03/2009	n/a		
IB/0016	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	02/02/2009	n/a		
II/0015	Update of the section 4.8 of the Summary of	18/12/2008	26/01/2009	SmPC and PL	Following a request from CHMP, the MAH provided an

	Products Characteristics regarding varicella zoster virus-naïve and low seropositive subjects further to the CHMP assessment of PSUR 3. The MAH took also the opportunity to update the details of the local representatives in Latvia and Malta in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet				overview of safety data from two clinical trials in varicella zoster virus (VZV) -naïve adults. Based on the review of clinical data 2.4 % of vaccinated subjects were found to be seronegative and additional 1.7% of patients were low-seropositive at the time of vaccination in one of the studies. This group of patients are considered to be at risk for developing varicella or other adverse experiences associated with wild type VZV infection. In terms of safety, systemic clinical adverse experiences reported were generally similar in incidence and spectrum to those reported by VZV-experienced subjects in this limited dataset. No subjects reported varicella-like or herpes zoster-like rashes. No serious vaccine-related adverse experiences were reported. The available safety information on VZV-seronegative and low seropositive adult subjects ?30 years old enrolled in clinical trials of a live attenuated varicella vaccine was included in the SPC.
II/0014	Changes to the manufacturing process of the drug product. Change(s) to the manufacturing process for the finished product	20/11/2008	01/12/2008		
II/0010	Change(s) to the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	23/10/2008	28/10/2008		

II/0009	Change(s) to the manufacturing process of the active substance Change(s) to the test method(s) and/or specifications for the active substance	23/10/2008	28/10/2008		
II/0013	Update of Summary of Product Characteristics and Package Leaflet to add the adverse events pyrexia, hypersensitivity reactions including anaphylactic reactions and rashes in section 4.8 "Undesirable effects" of the SPC following a review of adverse events reported in the 2nd PSUR (2 November 2006 to 1 May 2007) as requested by the CHMP. The PL has been updated accordingly. Furthermore the MAH took the opportunity to update the contact details of the local representatives in Denmark and Malta. Update of Summary of Product Characteristics and Package Leaflet	24/07/2008	01/09/2008	SmPC and PL	As a result of monitoring of the adverse events occurring after administration of Zostavax the CHMP considered that the four adverse event terms: pyrexia, hypersensitivity, anaphylactic reaction and rash should be added to the SPC under the Post Marketing Reports section of the "undesirable effects" Section 4.8 of the SPC. Pyrexia was observed in 17 cases during the observation period from market introduction to 19 October 2007, with an onset occurring in close temporal relationship of a few hours to one week. Hypersensitivity was reported in 8 cases during this period, including immediate anaphylactic reactions requiring immediate treatment, as well as hypersensitivity reactions occurring few hours or days after vaccination. For the time period from market introduction to 31 March 2008 post marketing reports with the following preferred terms: rash pruritic (46 reports), rash popular (17 reports), rash maculo-papular (7 reports), rash macular (14 reports), rash generalised (38 reports), and rash erythematous (14 reports) have been observed. The CHMP considered that the data and analyses provided were considered satisfactory to support the proposed changes.

II/0012	Addition of an alternate site (to perform manufacturing and release testing). Change(s) to the test method(s) and/or specifications for the finished product	24/07/2008	31/07/2008		
II/0011	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.8 and 5.1 of the SPC to include the information on the safety and immunogenicity of Zostavax when administered to patients with a history of Herpes Zoster (HZ) prior to administration based on a clinical study in subjects with a previous episode of HZ. The MAH also took the opportunity to update the PL to include a description of the medicinal product before reconstitution and a statement regarding the inspection of the vaccine components before use. In addition, the MAH took the opportunity to update the contact details of local representatives (AT, CZ and DK) in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	28/07/2008	SmPC and PL	The inclusion of additional information on the safety and immunogenicity of Zostavax was supported by a double-blind, placebo-controlled, randomised, crossover, multicentre phase III study to evaluate the safety, tolerability and immunogenicity of one dose of Zostavax in subjects who experienced a previous episode of HZ. Subjects in the first group received at the beginning and at week 4 of the trial a single, subcutaneous injection of Zostavax and subjects in the second group received placebo. All subjects were followed for serious adverse experiences, for exposure to varicella or HZ, or development of any varicella/varicella-like or HZ/HZ-like rashes, as well as any other adverse experiences for 28 days after each injection. The study data indicated that the proportions of subjects reporting specific systemic clinical adverse experiences were generally comparable between the two vaccination groups and strata. Zostavax was generally well tolerated when administered to HZ history-positive adults ? 50 years of age. The CHMP further considered that the frequencies and types of adverse experiences reported in this study were consistent with what has been seen in other Zostavax studies. Overall, following administration of Zostavax in patients

					with HZ-positive history no significant differences in safety data of patient in relation to the time period passed between the previous HZ infections could be identified. The CHMP therefore supported the proposed change of the Product Information.
IA/0008	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	22/01/2008	n/a		
II/0006	Quality changes	20/09/2007	25/09/2007		
II/0003	Extension of Indication Extension of Indication	21/06/2007	24/07/2007	SmPC, Annex II and PL	See Scientific Discussion EMEA-H-674-II-003
IA/0005	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	22/05/2007	n/a		
II/0004	To update sections 4.5, 4.8 and 5.1 of the SPC with regards to concomitant administration of ZOSTAVAX and inactivated influenza vaccine following the results of a clinical study, which evaluated the safety and efficacy of concomitant administration of ZOSTAVAX with flu vaccine in adults =50 years of age. The MAH also took the opportunity to update the contact details of local representatives in the Package Leaflet. In addition the MAH completed the list of local representatives in the Package Leaflet to include the two new EU Member States (Bulgaria and Romania) and changed the format according to the	16/11/2006	03/01/2007	SmPC and PL	Both, Zostavax and influenza vaccines are indicated for older persons carrying particular risks for herpes zoster and influenza. Influenza vaccines are specifically recommended for individuals older than 60 years of age, while specific recommendations for Zostavax do not yet exist. The concept to administer both vaccines during the same consultation was considered reasonable and was clinically investigated. As no differences with regard to immunogenicity and safety were observed in the concomitant versus sequential use of both vaccines, the CHMP considered that Zostavax can be given concomitantly with inactivated influenza vaccines licensed in the EU. The Summary of Product Characteristics and Package Leaflet

	latest EMEA/QRD template Update of Summary of Product Characteristics and Package Leaflet				were updated to reflect these changes.
II/0002	Change(s) to shelf-life or storage conditions	16/11/2006	03/01/2007	SmPC, Labelling and PL	The Marketing Authorisation Holder applied to change the current frozen formulation of the finished product into a refrigerator-stable formulation to be stored at 2ºC-8ºC.
IA/0001	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	22/06/2006	n/a		