Bridion

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0047	Extension of indication to include treatment of paediatric patients from birth to less than 2 years of age with Bridion based on final results from paediatric study PN169 (MK-8616-P169); this is a Phase 4 double-blinded, randomized, active comparator-controlled clinical trial to study the	12/12/2024	28/01/2025	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Bridion-H-C-000885-II-0047'.

[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).

	efficacy, safety, and pharmacokinetics of sugammadex (MK-8616) for reversal of neuromuscular blockade in paediatric participants aged birth to <2 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, to implement minor editorial corrections and to update the information intended for healthcare professionals (HCPs) at the end of the Package Leaflet. The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/2799/ 202401	Periodic Safety Update EU Single assessment - sugammadex	17/10/2024	12/12/2024	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2799/202401.
IAIN/0045	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	13/06/2023	20/06/2024	Annex II and PL	
N/0044	Minor change in labelling or package leaflet not	22/12/2022	20/06/2024	PL	

	connected with the SPC (Art. 61.3 Notification)				
IB/0043/G	This was an application for a group of variations. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	16/03/2022	n/a		
II/0042	C.I.3 type II to update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to change posology recommendations and update safety, efficacy and pharmacokinetic information in children and adolescents (2-17 years) following EMEA/H/C/0885/P46/025 and based on final results from study P089MK8616. This is a Phase 4 Double-Blinded, Randomized, Active Comparator-Controlled Clinical Trial to Study the Efficacy, Safety and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants. In addition, the MAH took the opportunity to implement some minor editorial changes throughout the Product Information (section 4.4 of Annex I and Annex II). The Package Leaflet is updated in accordance and the MAH took the opportunity to update the list of local representatives. Version 8.0 of the RMP is	16/12/2021	24/01/2022	SmPC and PL	In section 4.2, posology recommendations have been updated for routine reversal of reversal of rocuronium in children and adolescents (2 to 17 years of age). Section 4.8 has been updated to inform that in studies of paediatric patients 2 to 17 years of age, the safety profile of sugammadex (up to 4 mg/kg) was generally similar to the profile observed in adults. Section 5.1 has been updated to provide new efficacy data from a trial investigating sugammadex versus neostigmine as a reversal agent for neuromuscular blockade induced by rocuronium or vecuronium in in children and adolescents (2 to 17 years of age). In section 5.2, pharmacokinetic parameters stratified by age and renal function has been updated. The Package Leaflet (PL) is updated accordingly. For more information, please refer to the Summary of Product Characteristics.

	recommended to incorporate changes due to the completeness of PN089 and the MAH took the opportunity to update the RMP with information on completed clinical studies PN089, PN146 and PN145 and to implement the RMP GVP Module V Rev 2 template. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
II/0039	Update of sections 4.8 and 5.1 of the SmPC in order to update information on safety profile in American Society of Anesthesiologists (ASA) Class 3 or 4 patients (patients with severe systemic disease or patients with severe systemic disease that is a constant threat to life) based on final results from study 8616-P145, an interventional safety study of sugammadex for the reversal of neuromuscular blockage induced by rocuronium or vecuronium in adult ASA 3-4 participants. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/06/2021	24/01/2022	SmPC	Update of sections 4.8 and 5.1 in the SmPC to inform that based on the final results of a trial including ASA Class 3 and 4 patients, the overall adverse reaction profile of sugammadex - including the incidence of treatment-emergent arrhythmias- in ASA Class 3 and 4 patients is expected to be similar to the adults patients included in the pooled phase 1 to 3 studies. No dosage adjustment is necessary. For more information, please refer to the Summary of Product Characteristics.
II/0041/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	28/05/2021	n/a		

	B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IA/0040/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.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	23/02/2021	n/a		
IA/0037	A.7 - Administrative change - Deletion of manufacturing sites	20/10/2020	n/a		
II/0036	The MAH conducted a dedicated phase 4 clinical trial in morbidly obese patients and the results show that adverse reaction profile was generally similar to the profile in adult patients in pooled Phase 1 to 3 studies. Consequently sections 4.2, 4.8, 5.1 and 5.2 of the SmPC were updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	02/04/2020	16/07/2021	SmPC, Annex II, Labelling and PL	Section 4.2 of the SmPC was updated as follows: Obese patients: In obese patients, including morbidly obese patients (body mass index ≥ 40 kg/m2), the dose of sugammadex should be based on actual body weight. The same dose recommendations as for adults should be followed. Section 4.8 of the SmPC was updated as follows:

	data				Morbidly obese patients In one dedicated clinical trial in morbidly obese patients, the adverse reaction profile was generally similar to the profile in adult patients in pooled Phase 1 to 3 studies (see Table 2). Section 5.1 of the SmPC was updated as follows: Morbidly obese patients: A trial of 188 patients who were diagnosed as morbidly obese investigated the time to recovery from moderate or deep neuromuscular blockade induced by rocuronium or vecuronium. Patients received 2 mg/kg or 4 mg/kg sugammadex, as appropriate for level of block, dosed according to either actual body weight or ideal body weight in random, double-blinded fashion. Pooled across depth of block and neuromuscular blocking agent, the median time to recover to a train-of-four (TOF) ratio ≥ 0.9 in patients dosed by actual body weight (1.8 minutes) was statistically significantly faster ($p < 0.0001$) compared to patients dosed by ideal body weight (3.3 minutes). Section 5.2 of the SmPC was updated as follows: Obesity: In one clinical study in morbidly obese patients, sugammadex 2 mg/kg and 4 mg/kg was dosed according to actual body weight (n=76) or ideal body weight (n=74). Sugammadex exposure increased in a dose-dependent, linear manner following administration according to actual body weight or ideal body weight. No clinically relevant

					differences in pharmacokinetic parameters were observed between morbidly obese patients and the general population.
IB/0035/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	30/09/2019	n/a		
PSUSA/2799/ 201901	Periodic Safety Update EU Single assessment - sugammadex	05/09/2019	n/a		PRAC Recommendation - maintenance
IB/0034/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.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	11/06/2019	n/a		

	material/intermediate				
IB/0033/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement	11/06/2019	n/a		

	or addition) B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
IB/0031	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	26/03/2019	23/04/2020	SmPC, Labelling and PL	
T/0030	Transfer of Marketing Authorisation	13/06/2018	30/07/2018	SmPC, Labelling and PL	
IB/0029	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/02/2017	n/a		
IA/0028	A.7 - Administrative change - Deletion of manufacturing sites	02/12/2016	26/07/2017	Annex II and PL	
PSUSA/2799/201601	Periodic Safety Update EU Single assessment - sugammadex	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0027	B.II.a.z - Change in description and composition of the Finished Product - Other variation	31/08/2016	26/07/2017	SmPC and Labelling	
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2016	26/07/2017	Labelling and PL	
II/0024	Update of section 4.4 with additional information on recurrence of neuromuscular blockade and waiting	24/09/2015	26/02/2016	SmPC and PL	In this variation the PI was updated with the information that in clinical studies with subjects treated with

	times for re-administration with neuromuscular blocking agents and section 4.8 of the SmPC in order to update the safety information. Furthermore, minor updates have been made to sections 4.2, 4.4, 5.3 and 6.6 of the SmPC. The Package Leaflet is updated accordingly. Additionally, editorial changes were introduced throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				rocuronium or vecuronium, where sugammadex was administered using a dose labelled for the depth of neuromuscular blockade, an incidence of 0.20% was observed for recurrence of neuromuscular blockade as based on neuromuscular monitoring or clinical evidence. The use of lower than recommended doses may lead to an increased risk of recurrence of neuromuscular blockade after initial reversal and is not recommended.
II/0022	Update of section 4.8 of the SmPC based on the outcomes of this hypersensitivity confirmation study (Protocol P101 study). The MAH is also taking the opportunity to update the Portugal contact details in section 6 of the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2015	26/02/2016	SmPC and PL	
II/0021/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/	23/04/2015	n/a		

	immunological medicinal products B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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 B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation				
II/0023	Update section 5.2 of the SmPC in order to add information based on the outcomes of the new renal PK study. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	26/02/2015	26/02/2016	SmPC	

	data				
II/0019	Update of section 5.2 of the SmPC based on a review of bioanalytical data, in order to amend the information on pharmacokinetic parameters in the general population and in patients with renal impairment Furthermore, the MAH took the opportunity to implement editorial changes throughout the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	06/02/2015	SmPC, Labelling and PL	The CHMP considered the deficiencies in the latest pharmacokinetic (PK) modelling used to define the pharmacokinetic properties of Bridion. The previous model was considered to better predict the pharmacokinetic properties of the product and therefore was considered as the basis for the product information.
IG/0404	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	14/02/2014	n/a		
IG/0366	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	08/11/2013	n/a		
T/0017	Transfer of Marketing Authorisation	29/08/2013	09/10/2013	SmPC, Labelling and PL	
IB/0016	Update of section 4.4 of the SmPC following the outcome of the FU2 V-021.2 (CSR P0738 –	27/07/2013	09/10/2013	SmPC	

	'Hemostasis'). C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
R/0013	Renewal of the marketing authorisation.	25/04/2013	21/06/2013	SmPC and PL	Based on the review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considered that the risk-benefit balance of Bridion in the treatment of neuromuscular blockade induced by rocuronium or vecuronium remains favourable and therefore recommended the renewal of the marketing authorisation. The product information was updated to include bronchospasm and pulmonary obstructive events as possible manifestations of hypersensitivity reactions, in line with PRAC recommendations on a signal from post-marketing data. In addition, the SmPC was updated in order to highlight the potential of bleeding complications in patients with severely impaired liver function and related coagulation disorder referring healthcare professionals to the existing warning on effects of sugammadex on blood clotting.
II/0015	Update of sections 4.4 and 4.8 of the SmPC in order to add information about "marked bradycardia and bradycardia with cardiac arrest" and to introduce new precautions relevant to the prescriber. The Package Leaflet was updated accordingly. Furthermore, the Product Information (PI) was	30/05/2013	09/10/2013	SmPC and PL	The CHMP considered the cases of marked bradycardia reported in the post-marketing setting, including the small number of cases leading to cardiac arrest and was of the view that a causal relationship between sugammadex administration and bradycardia cannot be excluded. The data from phase 1-3 clinical trials also suggested that a

	brought in line with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				significant decrease in heart rate was more common in patients who received sugammadex than in those who received placebo. Overall, the CHMP concluded that the following information should be added in section 4.4 of the SmPC: In rare instances, marked bradycardia has been observed within minutes after the administration of sugammadex for reversal of neuromuscular blockade. Bradycardia may occasionally lead to cardiac arrest. Patients should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade. Treatment with anti-cholinergic agents such as atropine should be administered if clinically significant bradycardia is observed. The Package Leaflet and section 4.8 of the SmPC were updated accordingly.
IA/0014/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 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)	20/12/2012	n/a		
II/0011	Update of sections 4.2 and 4.4 of the SmPC in order to add information on waiting times for re-administration of rocuronium or vecuronium after reversal with sugammadex. In addition, sections 4.2 and 4.4 of the SmPC were updated to amend the	20/09/2012	25/10/2012	SmPC	This update of Product information followed a review of data from a clinical trial in healthy volunteers evaluating the onset times of neuromuscular blockade after re-administration of rocuronium or vecuronium at various time-points after administration of sugammadex to reverse

	period for potential displacement interactions after sugammadex administration. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				the initial neuromuscular blockade. In addition, modelling analyses were included on re-administration of rocuronium to support the proposed waiting time in subjects with and without renal impairment. The CHMP considered that the data presented by the MAH were of clinical relevance to the anaesthetists and provided sufficient evidence to be reflected in the product information. The CHMP also considered the updated pharmacokinetic model as basis for a change in the estimated half-life of sugammadex and consequently in the time during which displacement reactions may take place.
IG/0184	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/08/2012	n/a		
II/0010	Update of section 4.4 of the SmPC in order to delete the precautionary text related to the QTc interval prolongation. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to add the list of local representatives to the Package Leaflet. Furthermore, the MAH brought the Product Information in line with the latest QRD template version 8.1. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/06/2012	23/07/2012	SmPC, Annex II, Labelling and PL	This update of Product Information followed a review of QT prolongation data from dedicated QT/QTc clinical trials in healthy voluneers, meta-analysis of phase 2/3 trials with pre-specified ECG assessments and additional clinical information (pre- and post-marketing) on pro-arrhythmic events. The CHMP considered that the data presented by the MAH provided sufficient evidence to conclude that sugammadex has no clinically meaningul effect on QTc interval when administered alone or in combination with anaesthetics such as rocuronium, vecuronium, propofol and sevoflurane and agreed on deleting the text regarding QT interval prolongation fro the SmPC section 4.4 and Package Leaflet section 2.
II/0008/G	This was an application for a group of variations. Update of sections 4.2, 4.4, 4.9, 5.1 and 5.2 of the SmPC in order to add information on severe renal	19/01/2012	27/02/2012	SmPC, Annex II and PL	The MAH submitted clinical trial data on pharmacokinetics, efficacy and safety in a population of patients with severe renal impairment, including data on dialysability of sugammadex. The CHMP considered the increased

	impairment based on clinical trial data. Update of section 5.2 of the SmPC based on a fulfilled FUM 002 in order to reflect PK-PD modelling, providing further relevant information on severe renal impairment. Update of section 4.8 of the SmPC in order to add information on hypersensitivity based on clinical trial data. The Package Leaflet is updated in accordance. Update of sections 4.4 and 4.5 of the SmPC to add information on haemostasis based on a fulfilled FUM 005. Furthermore, the Product Information is being brought in line with the QRD template version 7.3, integrating data on fertility assessed in the context of the initial MAA in section 4.6 of the SmPC. The MAH also took the opportunity to remove reference to the version of the DDPS from the Annex II, to update the RMP version identifier and to make minor typographical corrections throughout the Product Information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				exposure to sugammadex, modestly longer recovery from neuromuscular blockade relative to patients without severe renal impairment and the safety information available and concluded that benefit-risk balance in patients with severe renal impairment remains unfavourable. This position also applies to patients with severe renal impairment requiring dialysis and this was specifically reflected in the Product Information. Based on the dialysability data, the CHMP considered that removal of sugammadex by dialysis would be feasible, but highlighted the variability of the data. In general, high flux dialysis showed better results than low flux dialysis and the CHMP concluded that results with high flux dialysis are of relevance to the prescriber in the context of overdose. Hypersensitivity was already listed in the Product Information. Based on data from a new clinical trial in healthy volunteers, the CHMP agreed that a subparagraph on hypersensitivity in healthy volunteers should be added, including frequencies of hypersensitivity reactions reported and reflecting the dose-dependent trend observed. The MAH proposed that the text regarding aPTT and PT prolongation be adapted to more accurately reflect the supporting data, with conclusions based upon maximum mean changes. The CHMP was of the view that the respective update of the Product Information was supported by the data available. Non-clinical data on fertility were evaluated as part of the initial MAA and the subheading “Fertility” was now included in the Product Information to follow the QRD template version 7.3. The following text was added into section 4.6 of the SmPC: “The effects with sugammadex on human fertility have not

					been investigated. Animal studies to evaluate fertility do not reveal harmful effects.”
IG/0117/G	This was an application for a group of variations. 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.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	18/11/2011	18/11/2011	Annex II	
II/0007	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	03/11/2010	SmPC, Annex II and PL	Sections 4.4 and 4.8 of the SmPC and section 4 of the Package Leaflet were revised to reflect data on the possibility of drug hypersensitivity reactions. The update was warranted by newly reported anaphylactic reactions that were previously not listed. The MAH also updated the Risk Management Plan with the current post-marketing data on anaphylaxis and upgraded hypersensitivity from a potential to an identified risk; subsequently, Annex II was updated with respect to the new version identifier of the latest Risk Management Plan.
II/0001	Update of Summary of Product Characteristics (Sections 4.4 and 4.5) and Package Leaflet (Section	22/04/2010	02/06/2010	SmPC and PL	The product information was updated to reflect data on the effects of sugammadex on hemostasis. These data

	2). Update of Summary of Product Characteristics and Package Leaflet				originated from a clinical trial requested by the CHMP at the time of granting the marketing authorisation, from further in vitro studies and experiments and from two analyses of bleeding complications in clinical studies with sugammadex. The CHMP concluded that the evidence currently available indicates an effect of sugammadex on hemostasis parameters. The MAH agreed with the CHMP on a more specific wording in the product information identifying situations of increased bleeding risks where caution should be exercised. Sections 4.4 and 4.5 of the SPC were updated to reflect these findings and the Package Leaflet was amended accordingly. Further to their assessment, the CHMP also requested that the overall effect on blood coagulation of sugammadex co-administered with acetylsalicylic acid should be studied with up-to-date methods and the results should be provided for evaluation.
II/0003	Update of Summary of Product Characteristics (Sections 4.4 and 4.5) and Package Leaflet (Section 2). Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	27/04/2010	SmPC and PL	The product information was updated to reflect the outcome of an interaction study performed as a follow-up measure as requested by the CHMP. This study was designed to investigate the potential of diclofenac and flucloxacillin to displace rocuronium or vecuronium from the complex with sugammadex. The data provided by the MAH revealed no re-occurrence of the neuromuscular blockade through displacement and, following CHMP assessment, the MAH was requested to update the product information accordingly. In addition to the interaction study results, the MAH also

					provided data pooled from several clinical trials looking at the re-occurrence of the neuro-muscular blockade after sugammadex reversal in the peri-operative setting with administration of various drugs. No interaction issues were identified, which was in line with the MAH interaction strategy (based on affinity constants determined) and no update to the product information was warranted. Additional information regarding fusidic acid use in the post-operative phase (i.e. that neuro-muscular blockade re-occurrence is not expected) was accepted by the CHMP as justified by the pharmacokinetic data available.
II/0002	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the contact details of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number. At the same time, the updated version number of the RMP following the PSUR assessment is being introduced. Update of DDPS (Pharmacovigilance)	21/01/2010	09/02/2010	Annex II	The DDPS has been updated (version 7, December 2009) to reflect the change of contact details 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 including the new version number of the agreed DDPS. At the same time, the updated version number of the RMP following the PSUR assessment is being introduced. The CHMP considers that the Pharmacovigilance System as described by the MAH is acceptable.
IB/0004	To add a new specification for an intermediate of the active substance To change an already approved test method To add new test methods IA_13_a_Change in test proc. for active substance - minor change IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	02/02/2010	n/a		

	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter				
IA/0006	To delete a manufacturing site responsible for secondary packaging IA_09_Deletion of manufacturing site	22/12/2009	n/a		
IA/0005	To change the name of a manufacturer of the active substance and the finished product. IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	22/12/2009	n/a		