Caelyx pegylated liposomal

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/0107	Submission of an updated RMP version 6.3 in order to align to GVP Module V Revision 2 requirements, as requested as part of the outcome for EMEA/H/C/PSUSA/00001172/202111. C.I.11.b - Introduction of, or change(s) to, the	11/01/2024	n/a		Submission of an updated RMP version 6.1 in order to align to GVP Module V Revision 2 requirements, following a request received within the Assessment Report for procedure EMEA/H/C/PSUSA/00001172/202111. The requested variation proposed amendments to the Risk Management Plan (RMP).

[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).

	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				
PSUSA/1172/ 202211	Periodic Safety Update EU Single assessment - doxorubicin	22/06/2023	25/08/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1172/202211.
IB/0106/G	This was an application for a group of variations. B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	31/03/2023	25/08/2023	Annex II and PL	

	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.a - Replacement or addition of a				

	manufacturing site for the FP - Secondary packaging site B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation				
IB/0104	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	05/01/2023	25/08/2023	SmPC and PL	
II/0103	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	15/12/2022	n/a		
PSUSA/1172/ 202111	Periodic Safety Update EU Single assessment - doxorubicin	07/07/2022	n/a		PRAC Recommendation - maintenance
IA/0102	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)	09/05/2022	n/a		
IA/0101	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	06/04/2022	n/a		
IA/0099	A.7 - Administrative change - Deletion of manufacturing sites	08/11/2021	n/a		
T/0098	Transfer of Marketing Authorisation	28/07/2021	20/08/2021	SmPC, Labelling and	

				PL	
II/0094	Update of sections 4.2 and 4.8 of the SmPC in line with the SmPC guideline. In addition, the MAH took the opportunity to update the PI in line with the QRD template version 10.1 and with the EDQM standard terms. Furthermore, the list of local representatives in the Package Leaflet is updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/12/2020	18/01/2021	SmPC, Annex II, Labelling and PL	PRAC requested the MAH to submit a variation application to revise Section 4.8 of the EU Summary of Product Characteristics (SmPC) in accordance with the latest EU Guideline on SmPC. Several tables of ADRs were mentioned in the section 4.8 of SmPC despite of similar indications of Caelyx and should have been merged in one table only. Additionally, some ADRs were listed standalone outside the tables in the document making the Section 4.8 unclear for healthcare professionals. Pooled analysis of the clinical trials data was used to establish the frequency of ADRs. All these issues have been resolved.
IB/0097	B.III.1.a.5 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate of a non-sterile AS that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free	12/08/2020	n/a		
IA/0096	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	08/07/2020	n/a		
IA/0095	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	26/03/2020	n/a		

N/0093	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/03/2020	19/10/2020	Labelling	
IAIN/0092	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	30/10/2019	19/10/2020	SmPC, Labelling and PL	
PSUSA/1172/ 201811	Periodic Safety Update EU Single assessment - doxorubicin	25/07/2019	23/09/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1172/201811.
IA/0091	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/08/2019	n/a		
IB/0089/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.a - Change to importer, batch release	08/07/2019	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)				

	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished				

	product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IA/0090	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	31/05/2019	n/a		
IB/0086	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	20/12/2018	n/a		
IA/0087	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	23/11/2018	n/a		
N/0085	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2018	17/04/2019	PL	
IB/0084	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/05/2018	17/04/2019	SmPC, Labelling and PL	

IB/0083	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/01/2017	24/03/2017	SmPC, Annex II, Labelling and PL	
PSUSA/1172/ 201511	Periodic Safety Update EU Single assessment - doxorubicin	07/07/2016	n/a		PRAC Recommendation - maintenance
II/0082	Update of section 4.8 of the SmPC to remove the specific time-frame for initiation of treatment for palmar-plantar erythrodysesthesia (PPE). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the Package Leaflet and to update the names of the local representatives in the Package Leaflet for Latvia, Estonia and Lithuania. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/04/2016	24/03/2017	SmPC and PL	N/A
IA/0079	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	28/08/2015	n/a		
IB/0080	B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	12/08/2015	n/a		
II/0077	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/04/2015	31/03/2016	SmPC and PL	

IG/0531	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/03/2015	n/a		
N/0076	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/01/2015	31/03/2016	PL	
IB/0075/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.III.2.c - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change	12/11/2014	n/a		

	in specifications from a national pharmacopoeia of a Member State to the Ph. Eur. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0074/G	This was an application for a group of variations. To add sites responsible for the manufacturing, testing, primary packaging and release of the finished product and to make minor changes in the immediate packaging of the finished product. 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.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.c.z - Change in control of excipients in the Finished Product - Other variation B.II.c.z - Change in control of excipients in the Finished Product - Other variation	23/10/2014	n/a		

	B.II.e.1.z - Change in immediate packaging of the finished product - Other variation B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
II/0072/G	This was an application for a group of variations. To change the manufacturing process of the finished product. B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.z - Change in manufacture of the Finished Product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	26/06/2014	n/a		

	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.e.1.z - Change in immediate packaging of the finished product - Other variation				
IA/0073	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	05/06/2014	n/a		
IA/0071	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)	20/02/2014	n/a		
IA/0070	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	11/12/2013	n/a		
IA/0069/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	05/11/2013	n/a		

	(excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
II/0067/G	This was an application for a group of variations. - to add an alternative manufacturing site for the finished product, - to change the batch size at the new alternative manufacturing site, - to introduce minor changes in the manufacture of the finished product, - to change the specification of the vial stoppers used in the new site, - to change in the specification parameters for 10 ml glass vials. 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	19/09/2013	n/a		

	aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation				
II/0066	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning regarding the incidence of "secondary oral neoplasms" following review of the MAH's safety database. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to add the details of the Croatian representative. Furthermore, the PI is being brought in line with the latest QRD template version 9.0 and some editorial changes were made (re-arrangement of information). The requested variation proposed amendments to the Summary of Product Characteristics, Annex II,	19/09/2013	11/09/2014	SmPC, Annex II, Labelling and PL	Based on a comprehensive review and analysis of secondary oral malignancy reported with pegylated liposomal doxorubicin (PLD), sections 4.4 and 4.8 of the SmPC have been updated in order to include secondary oral neoplasms as an ADR and to include a recommendation for oral examinations to check for the presence of any oral ulceration or oral discomfort as a precaution. The Package Leaflet has been updated accordingly.

	Labelling and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
II/0065/G	This was an application for a group of variations. This was an application for a group of variations - to replace the current manufacturer for sterile filtration and primary packaging for the finished product with a new one - to introduce changes in the sterile filtration and primary packaging manufacturing steps that are performed at the new site, including changes to the in-process control tests and limits in the manufacture of the finished product - to introduce a new testing site for the finished product - to introduce a new raw material and active substance testing site. 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	18/10/2012	18/10/2012		

	aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
IA/0064	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	03/09/2012	n/a		
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
IB/0062	C.I.8.b - Introduction of a new Pharmacovigilance	31/05/2012	29/10/2012	Annex II	

	system - which has been assessed by the relevant NCA/EMA for another product of the same MAH				
A20/0061	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17 November 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in Bedford, Ohio (USA).	15/03/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/00089/A-20/061
IA/0060	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	11/11/2010	n/a		
IA/0059	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	11/11/2010	n/a	Annex II and PL	
T/0057	Transfer of Marketing Authorisation	03/09/2010	27/09/2010	SmPC, Labelling and PL	
IA/0058	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	15/09/2010	n/a		

IB/0056/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	06/07/2010	n/a		
II/0055	To change the drug product specification. Quality changes	19/11/2009	25/11/2009		
IB/0054	IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product	24/08/2009	n/a		
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2009	n/a	PL	
IA/0053	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	10/02/2009	n/a		
IB/0051	IA_19_a_Change in specification of an excipient - tightening of specification limits IB_20_c_Change in test procedure for an excipient - other changes	28/05/2008	n/a		
IA/0050	IA_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	21/02/2008	n/a		
II/0045	In combination with bortezomib for the treatment of	15/11/2007	14/12/2007	SmPC, Annex	Please refer to Scientific Discussion AR-H-089-II-45

	progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant. Extension of Indication			II and PL	
IA/0049	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	29/10/2007	n/a		
IB/0047	IA_19_a_Change in specification of an excipient - tightening of specification limits IB_20_c_Change in test procedure for an excipient - other changes	05/10/2007	n/a		
IB/0048	IB_20_c_Change in test procedure for an excipient - other changes	03/08/2007	n/a		
II/0046	Quality changes	19/07/2007	01/08/2007		
II/0041	Update of Summary of Product Characteristics and Package Leaflet	26/04/2007	30/05/2007	SmPC and PL	Update of section 4.8 of the SPC and Section 4 of the PL. with information on cases of thrombophlebitis and venous thrombosis, as well as rare cases of pulmonary embolism. In summary, of 231 cases of venous thromboembolism in the MAH's Global Pharmacovigilance database, only 164 are considered confirmed cases. Of the 164 confirmed cases, the majority (i.e.134 cases) were not considered to be possibly or probably related to Caelyx treatment. Therefore, in only 30 confirmed cases was there sufficient evidence to assign a possible or probable causal association

					(possible causality in 28 and probable causality in 2). Notwithstanding the fact that it may not be easy to clearly show drug-specific causality in this application because of malignant disease and concomitant antineoplastic agents, the MAH's venous thromboembolism event rate for Caelyx still falls below the majority of the rates in similar malignant disease-specific populations the published literature. Because both DVT and PE are usually serious events, and PE carries a high fatality rate, the SPC is updated with the following statement: "In patients treated with Caelyx, cases of venous thromboembolism, including thrombophlebitis, venous thrombosis and pulmonary embolism have been seen uncommonly. However, because patients with cancer are at increased risk for thromboembolic disease, a causal relationship cannot be determined" based on the available information.
IA/0044	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	16/04/2007	n/a		
IB/0043	IB_38_c_Change in test procedure of finished product - other changes	12/02/2007	n/a		
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/01/2007	n/a	PL	
II/0040	Update of Summary of Product Characteristics	21/09/2006	20/10/2006	SmPC	Addition of pre-clinical safety information to the SPC (section 5.3) regarding renal toxicity, as requested by the CHMP following the assessment of 2nd 5-year Renewal and

					the 8th PSUR.
R/0038	Renewal of the marketing authorisation.	23/03/2006	19/05/2006	SmPC, Annex II, Labelling and PL	
IB/0039	IB_38_c_Change in test procedure of finished product - other changes	11/04/2006	n/a		
IA/0037	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	22/09/2005	n/a		
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/06/2005	n/a	Labelling and PL	
IA/0035	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/03/2005	n/a		
II/0033	Update of or change(s) to the pharmaceutical documentation	20/01/2005	17/02/2005	SmPC	
II/0034	Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/11/2004	05/01/2005	SmPC, Annex II, Labelling and PL	
II/0032	Update of Summary of Product Characteristics	18/11/2004	05/01/2005	SmPC	
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/05/2004	n/a	PL	
IB/0030	IB_24_Change in synthesis or recovery of non-pharmacopoeial excipient (when descr. in dossier)	12/03/2004	n/a		

I/0029	18_Synthesis or recovery of non-pharmacopoeial excipients in the medicinal products	11/07/2003	15/07/2003		
I/0028	15_Minor changes in manufacture of the medicinal product	01/07/2003	08/07/2003		
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/02/2003	17/03/2003	PL	
I/0026	15_Minor changes in manufacture of the medicinal product 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	17/01/2003	24/01/2003		
II/0023	Extension of Indication	17/10/2002	10/01/2003	SmPC and PL	
I/0025	15_Minor changes in manufacture of the medicinal product	15/05/2002	17/05/2002		
I/0024	15_Minor changes in manufacture of the medicinal product	15/05/2002	17/05/2002		
I/0021	15_Minor changes in manufacture of the medicinal product	20/12/2001	21/01/2002		
I/0020	15_Minor changes in manufacture of the medicinal product	20/12/2001	21/01/2002		
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/01/2002	19/02/2002	PL	

R/0019	Renewal of the marketing authorisation.	31/05/2001	24/09/2001	SmPC, Annex II, Labelling and PL	
II/0017	Update of Summary of Product Characteristics and Package Leaflet	29/03/2001	05/07/2001	SmPC and PL	
I/0018	20_Extension of shelf-life as foreseen at time of authorisation	26/02/2001	27/04/2001	SmPC	
II/0013	New presentation(s) Extension of Indication	29/06/2000	24/10/2000	SmPC, Labelling and PL	
II/0014	Update of Summary of Product Characteristics	17/02/2000	29/05/2000	SmPC	
I/0016	14_Change in specifications of active substance	18/02/2000	25/02/2000		
I/0015	11_Change in or addition of manufacturer(s) of active substance	26/01/2000	22/02/2000		
II/0012	Update of Summary of Product Characteristics and Package Leaflet	22/04/1999	26/07/1999	SmPC, Labelling and PL	
I/0011	16_Change in the batch size of finished product	03/07/1998	n/a		
I/0010	25_Change in test procedures of the medicinal product	13/11/1997	n/a		
I/0009	25_Change in test procedures of the medicinal product	13/11/1997	n/a		

I/0008	25_Change in test procedures of the medicinal product	13/11/1997	n/a		
I/0007	25_Change in test procedures of the medicinal product	13/11/1997	n/a		
I/0006	25_Change in test procedures of the medicinal product	13/11/1997	n/a		
I/0005	25_Change in test procedures of the medicinal product	13/11/1997	n/a		
II/0003	Update of Summary of Product Characteristics and Package Leaflet	16/04/1997	29/07/1997	SmPC and PL	
I/0004	03_Change in the name and/or address of the marketing authorisation holder	18/03/1997	07/05/1997	SmPC, Labelling and PL	
I/0002	01_Change following modification(s) of the manufacturing authorisation(s)	18/03/1997	07/05/1997	Annex II	
T/0001	Transfer of Marketing Authorisation	22/11/1996	18/02/1997	SmPC, Labelling and PL	