Hycamtin

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
IAIN/0103	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	26/09/2024		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).

WS/2691	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC in order to update recommendations on duration of contraception in males and females, in line with the SWP/NcWP recommendations (EMA/CHMP/SWP/74077/2020 rev. 1*) on the duration of contraception following the end of treatment with a genotoxic drug and based on the proposed wording suggested in the CMDh report for EMA/CMDh/409368/2021. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	04/07/2024		SmPC and PL	Women of childbearing potential should use effective contraceptive measures while being treated with topotecan and for 6 months following completion of treatment. Men are recommended to use effective contraceptive measures and to not father a child while receiving topotecan and for 3 months following completion of treatment.
N/0101	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/12/2023		PL	
N/0100	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/01/2023		PL	
T/0099	Transfer of Marketing Authorisation	14/10/2022	09/11/2022	SmPC, Labelling and PL	
IA/0097/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 -	05/09/2022	n/a		

	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				
IA/0098	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	31/08/2022	n/a		
IAIN/0096/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.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.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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/08/2022	09/11/2022	Annex II and PL	
IG/1521	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	23/06/2022	n/a		

	site				
IAIN/0094	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/06/2022	n/a		
IA/0093	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	17/05/2022	n/a		
IAIN/0092/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	18/03/2022	n/a		
IB/0091	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/10/2021	n/a		
IA/0090	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	20/08/2021	21/06/2022	SmPC and PL	
IAIN/0088/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 -	07/06/2021	21/06/2022	SmPC and PL	

	Replacement/addition of a site where batch control/testing takes place 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				
IA/0087	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	06/04/2021	n/a		
PSUSA/2997/ 202005	Periodic Safety Update EU Single assessment - topotecan	14/01/2021	n/a		PRAC Recommendation - maintenance
IA/0086	A.7 - Administrative change - Deletion of manufacturing sites	04/12/2020	18/01/2021	Annex II and PL	
IB/0085	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/10/2020	18/01/2021	SmPC, Annex II, Labelling and PL	
IA/0083/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.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	10/04/2020	n/a		

	specification limits				
IAIN/0082	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	23/01/2020	18/01/2021	Annex II and PL	
IAIN/0081	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	10/12/2019	n/a		
IAIN/0080/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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a	09/12/2019	n/a		

	manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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 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				
IAIN/0079/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)	17/09/2019	n/a		

	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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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				
IB/0078/G	This was an application for a group of variations. 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) B.II.d.2.z - Change in test procedure for the finished product - Other variation	23/08/2019	n/a		
IB/0077/G	This was an application for a group of variations. 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	31/07/2019	n/a		

	procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.z - Change in test procedure for the finished product - Other variation				
IG/0950	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)	18/06/2018	n/a		
T/0075	Transfer of Marketing Authorisation	20/03/2018	23/04/2018	SmPC, Labelling and PL	
II/0074	To update the section 4.8 (Undesirable effects) of the SmPC in order to add two new identified ADRs: GI perforation and Mucosal inflammation, which have been identified for Hycamtin in the post-marketing experience. The package leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0, to update section 6.6 of the SmPC to remove the sentence "Liquid waste may be flushed with large amounts of water" as per EMA request on 25-May-2015 and to correct the renewal date in the section 9 of the	28/09/2017	23/04/2018	SmPC, Annex II, Labelling and PL	Based on the cumulative review of the available data from post-marketing experience of Hycamtin, it can be concluded that there is sufficient evidence to support a possible association between topotecan treatment and gastrointestinal perforation and mucosal inflammation. Gastrointestinal perforation and Mucosal inflammation are added as a new adverse reactions with frequency 'not known' to SmPC section 4.8.

	SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/05/2017	23/04/2018	PL	
N/0072	Update of the package leaflet with revised contact details of the local representatives for France and Spain. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/07/2016	23/04/2018	PL	
IAIN/0071/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	11/05/2016	n/a		

	site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a				

	manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
PSUSA/2997/ 201505	Periodic Safety Update EU Single assessment - topotecan	14/01/2016	n/a		PRAC Recommendation - maintenance
IAIN/0069/G	This was an application for a group of variations. 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 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	13/07/2015	30/06/2016	Annex II and PL	
T/0068	Marketing Authorisation Transfer from Smithkline Beecham Ltd. to Novartis Europharm Limited. Transfer of Marketing Authorisation	07/04/2015	24/04/2015	SmPC, Labelling and PL	
IB/0067/G	This was an application for a group of variations.	13/10/2014	n/a		

	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.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.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				
II/0065	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	24/04/2015	SmPC, Labelling and PL	
IA/0066/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/06/2014	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0064	Update of sections 4.2, 4.4 and 5.2 of the SmPC to include information on patients with renal impairment following the completion of study 104864/722. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the MAH proposed this opportunity to bring the PI 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	24/10/2013	20/11/2013	SmPC, Annex II, Labelling and PL	Results of a cross-study analysis suggest that the exposure to topotecan lactone, the active moiety following topotecan administration, increases at decreased renal function. The recommended monotherapy dose of oral topotecan in patients with small cell lung carcinoma with a creatinine clearance between 30 and 49 ml/min is 1.9 mg/m2/day for five consecutive days. If well tolerated, the dose may be increased to 2.3 mg/m2/day in subsequent cycles (see section 5.2). Insufficient data are available to make a recommendation for patients with a creatinine clearance < 30 ml/min. Topotecan is not recommended to be used in these patients. Korean patients with renal impairment had generally higher exposure than non-Asian patients with the same degree of renal impairment. The clinical significance of this finding is unclear, but the data in Korean patients suggest that a

					further lowering of dose may be required in these patients. There is no data from Asian patients with renal impairment other than Koreans.
IG/0275	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2013	n/a		
N/0062	Update the contact details for the local representatives in Belgium and Luxembourg. Include other minor editorial changes to Danish, Finnish, Hungarian, Czech, Latvian and French translations of PL. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/02/2013	20/11/2013	Labelling and PL	
IG/0150/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.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	05/04/2012	n/a		
IG/0034/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance	06/01/2011	n/a	Annex II	

	system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system 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 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				
II/0059	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 Update to sections 4.2, 4.4 and 4.8 of the SmPC regarding severe bleeding, pancytopenia, potential	23/09/2010	28/10/2010	SmPC, Annex II and PL	Following the assessment of the 9th PSUR (PSU 014), the CHMP requested the MAH to submit cumulative reviews on fatal pulmonary events, fatal cases with febrile neutropenia, sepsis and septic shock, serious infections and fatal cases with thrombocytopenia and/or haemorrhages by indication, to discuss the need to update section 4.8 on the potential fatal outcome of interstitial lung disease and neutropenic complications such as sepsis and septic shock

	fatal outcome of sepsis and interstitial lung disease, dehydration as a consequence of severe diarrhoea as agreed by the CHMP following the assessment of FUM 019. Annex II has been updated in order to include the latest version number of the RMP (version 03).The MAH has taken the opportunity of this procedure to update the local representative contact details from Denmark and Cyprus, and to make further editorial amendments to the Product Information (SmPC, Annex II, Package Leaflet) as part of the PIM pre-migration exercise. 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				and if the dose reduction suggestions in section 4.2 of the SmPC in case of bone marrow toxicity should be revised. In their responses submitted as FUM 019, the MAH proposed to update the RMP and the SmPC concerning the risk of severe bleeding (associated with thrombocytopenia), potential fatal outcome of sepsis and interstitial lung disease, dehydration as a consequence of severe diarrhoea and additional information on proactive management of diarrhoea and management of severe diarrhoea, and pancytopenia. The MAH has hereby submitted a type II variation. The CHMP considered this type II variation acceptable and agreed on amendments to be introduced in the SmPC, Annex II and Package Leaflet and on the revised RMP.
II/0055	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number. Changes to QPPV Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II	The DDPS has been updated (version 7.2) 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.
IB/0058	To change impurities reference material used in the analytical methods for the determination of the Topotecan Hydrochloride and degradation products.	20/01/2010	n/a		

	IB_38_c_Change in test procedure of finished product - other changes				
IB/0057	To add an alternative supplier for the active substance used in the manufacture of the finished product. IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	20/01/2010	n/a		
IA/0056	IA_01_Change in the name and/or address of the marketing authorisation holder	10/12/2009	n/a	SmPC, Labelling and PL	
IB/0054	IB_38_c_Change in test procedure of finished product - other changes	16/07/2009	n/a		
IA/0053	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	30/04/2009	n/a		
II/0052	Update of Detailed Description of the Pharmacovigilance System (DDPS). Changes to QPPV Update of DDPS (Pharmacovigilance)	19/02/2009	17/03/2009	Annex II	This type II variation concerns an update of the Detailed Description of the Pharmacovigilance System (DPPS) in order to include a change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated to include the new version number of the agreed DDPS (version 6.2).
IA/0051	IA_28_Change in any part of primary packaging material not in contact with finished product	12/12/2008	n/a	PL	
II/0047	Update of Summary of Product Characteristics, Labelling and Package Leaflet	25/09/2008	30/10/2008	SmPC, Labelling and	This type II variation concerns an update of section 4.4 of the SPC with a warning regarding the underlying risk factors of interstitial lung disease, further to a request from

				PL	the CHMP. Topotecan has been associated with reports of interstitial lung disease, some of which have been fatal. Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic drugs and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease (e.g. cough, fever, dyspnoea and/or hypoxia), and topotecan should be discontinued if a new diagnosis of ILD is confirmed. The frequency of this adverse event has also been updated in section 4.8 of the SPC. The Package Leaflet has been updated accordingly. The MAH also proposed to update section 4.2 with a clarification regarding the use of prophylactic G-CSF for chemotherapy-induced neutropenia to align with the product information of the IV formulation . In addition, the MAH took the opportunity to make minor editorial changes to the SPC, labelling and Package Leaflet and to update the list of local representatives in the Package Leaflet.
IA/0050	IA_09_Deletion of manufacturing site	04/09/2008	n/a	Annex II and PL	
IA/0049	IA_11_b_Change in batch size of active substance or intermediate - downscaling	21/08/2008	n/a		
IA/0048	IA_11_b_Change in batch size of active substance or intermediate - downscaling	07/08/2008	n/a		
X/0044	X-3-iv_Change or addition of a new pharmaceutical form	24/01/2008	18/03/2008	SmPC, Labelling and	The MAH submitted an extension application to the marketing authorisation for a new pharmaceutical form/ new route of administration of Hycamtin, 0.25 mg and 1

				PL	mg hard capsules. From a clinical efficacy and safety perspective the application relied on data already assessed in relation to variation EMEA/H/C/123/II/34. The approved indication for capsules Hycamtin is restricted to small cell lung cancer (SCLC) and reads: HYCAMTIN capsules are indicated as monotherapy for the treatment of adult patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate (see section 5.1). Based on the data provided on quality, non-clinical and clinical aspects, the benefit-risk balance for the new oral capulse is considered favourable.
II/0046	Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	24/10/2007	SmPC and PL	This variation concerned an update of sections 4.4 and 4.8 of the SPC to include information on the risk of 'neutropenic colitis'. The Package Leaflet has been updated accordingly. Furthermore, the MAH took the opportunity to make some editorial changes to the SPC. Topotecan-induced neutropenia can cause neutropenic colitis. Fatalities due to neutropenic colitis have been reported in clinical trials with topotecan. In patients presenting with fever, neutropenia, and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered.
IA/0045	IA_11_b_Change in batch size of active substance or intermediate - downscaling	09/07/2007	n/a		
II/0042	Quality changes	24/05/2007	21/06/2007	SmPC and PL	The Marketing Authorisation Holder applied for the addition of a site for the manufacture and the primary packaging of

					Hycamtin 1 mg and 4 mg. Additionally, for this new site, changes have been carried out regarding batch size, in-process controls, manufacturing process and size of primary container (17 ml vial instead of 5 ml).
II/0041	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	24/01/2007	28/02/2007	SmPC and PL	The MAH applied for a type II variation to update section 4.8 of the SPC based on a review of cases of dehydration following treatment with topotecan. In addition, the MAH took the opportunity to update the Package Leaflet in line with the outcome of consultation with target patient groups on readability aspects, to add the contact details for Bulgaria and Romania to the list of local representatives and to update the contact details of the local representative in the UK. A review of Clinical trials in ovarian carcinoma and NSCLC including 1154 patients resulted in 38 reports of patients who experienced dehydration. Eight patients experienced grade 3 dehydration and 4 experienced grade 4 dehydration. Dehydration occurred in 0.8% of patients. Post-marketing data revealed 255 reported cases (in some cases more than one occurrence in each patient) of dehydration during topotecan use, 241 of which originated from clinical trials. 41 and 78 episodes were classified as being cases of grade 3 and 4 dehydration. Most commonly the cases occurred in relation to 'nausea', 'vomiting', 'diarrhoea' and/or 'anorexia' or other underlying conditions. In published literature cases of dehydration have been reported mostly without a demonstration of a direct causal relationship. The CHMP considers that the data available at present does not indicate a direct causal relationship between topotecan and dehydration, but rather an indirect effect. With

					reference to the product information, the Committee agreed with the MAH's proposal to update section 4.8 in order to further qualify the severity of the events that may lead to dehydration ('anorexia', 'nausea', 'vomiting' and 'diarrhoea'). The CHMP also considers the report of the consultation with target patient groups and the related proposed changes to be acceptable.
II/0040	Update of Summary of Product Characteristics. Update of Summary of Product Characteristics	18/10/2006	22/11/2006	SmPC	The MAH applied for a type II variation, upon request by the CHMP following the assessment of available paediatric data (OTH 010), to revise sections 4.2, 5.1 and 5.2 of the SPC to include information on use in paediatric patients based on the results from the Paediatric Oncology Group (POG) Studies 9275, 9275L and 9361. In addition, the MAH took the opportunity to make a few minor editorial changes to section 4.8 of the SPC. Topotecan was evaluated in a paediatric population; however, only limited data on efficacy and safety are available and therefore, no recommendation for treatment of children with Topotecan can be given. In an open-label trial involving children (n = 108, age range: infant to 16 years) with recurrent or progressive solid tumours, topotecan was administered at a starting dose of 2.0 mg/m2 given as a 30-minute infusion for 5 days repeated every 3 weeks for up to one year depending on response to therapy. Tumour types included were Ewing's Sarcoma/primitive neuroectodermal tumour, neuroblastoma, osteoblastoma, and rhabdomyosarcoma. Antitumour activity was demonstrated primarily in patients

					with neuroblastoma. Toxicities of topotecan in paediatric patients with recurrent and refractory solid tumours were similar to those historically seen in adult patients. In this study, forty-six (43%) patients received G-CSF over 192 (42.1%) courses; sixty-five (60%) received transfusions of Packed Red Blood Cells and fifty (46%) of platelets over 139 and 159 courses (30.5% and 34.9%) respectively. Based on the dose-limiting toxicity of myelosuppression, the maximum tolerated dose (MTD) was established at 2.0 mg/m2/day with G-CSF and 1.4 mg/m2/day without G-CSF in a pharmacokinetic study in paediatric patients with refractory solid tumours The pharmacokinetics of topotecan given as a 30-minute infusion for 5 days were evaluated in two studies. One study included a dose range of 1.4 mg/m2 to 2.4 mg/m2 in children (aged 2 up to 12 years, n = 18), adol
II/0038	Treatment, in combination with cisplatin, of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IV-B disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with combination. Extension of Indication	18/10/2006	22/11/2006	SmPC and PL	Please refer to the Scientific Discussion "Hycamtin-H-123-II-38".
R/0039	Renewal of the marketing authorisation.	21/09/2006	20/11/2006	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit-risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore

					considered that the benefit/risk profile of Hycamtrin continues to be favourable. The CHMP recommended that the renewal could be granted with unlimited validity. During the renewal procedure, changes were amade to the Product Information to bring it in line with the current EMEA/QRD template, SPC guideline and other relevant guideline(s), which were reviewed by QRD and accepted by the CHMP.
II/0034	Relapsed small cell lung cancer (SCLC) in patients for whom re-treatment with the first line regimen is not considered appropriate. Extension of Indication	17/11/2005	13/01/2006	SmPC, Labelling and PL	Please refer to the Scientific Discussion "Hycamtin-H-123-II-34".
IA/0037	IA_05_Change in the name and/or address of a manufacturer of the finished product	11/10/2005	n/a		
IA/0036	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	29/06/2005	n/a		
IA/0035	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	28/06/2005	n/a	Annex II and PL	
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/06/2004	n/a	PL	
II/0031	Change(s) to the manufacturing process for the active substance	25/09/2003	26/09/2003		

II/0030	Change(s) to container	24/07/2003	28/07/2003		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/06/2003	18/07/2003	PL	
I/0029	16_Change in the batch size of finished product	12/06/2003	17/06/2003		
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/01/2003	06/02/2003	PL	
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2002	11/12/2002	PL	
II/0022	Update of Summary of Product Characteristics	25/04/2002	30/07/2002	SmPC	
I/0024	03_Change in the name and/or address of the marketing authorisation holder	24/05/2002	30/07/2002	SmPC, Labelling and PL	
I/0023	01_Change in the name of a manufacturer of the medicinal product	24/05/2002	30/07/2002		
R/0021	Renewal of the marketing authorisation.	20/09/2001	04/02/2002	SmPC, Annex II, Labelling and PL	
II/0018	Update of Summary of Product Characteristics	31/05/2001	13/09/2001	SmPC	
I/0020	26_Changes to comply with supplements to pharmacopoeias	22/06/2001	05/07/2001		
I/0019	14_Change in specifications of active substance	07/06/2001	05/07/2001		

II/0017	Update of Summary of Product Characteristics	14/12/2000	20/03/2001	SmPC	
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/08/2000	25/09/2000	PL	
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/07/2000	25/09/2000	PL	
I/0014	15a_Change in IPCs applied during the manufacture of the product	10/05/2000	19/05/2000		
II/0010	New presentation(s)	21/10/1999	16/03/2000	SmPC, Labelling and PL	
I/0011	03_Change in the name and/or address of the marketing authorisation holder	19/10/1999	22/02/2000	SmPC, Labelling and PL	
I/0013	15a_Change in IPCs applied during the manufacture of the product	20/01/2000	09/02/2000		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/10/1999	22/02/2000	PL	
I/0009	15_Minor changes in manufacture of the medicinal product	07/05/1999	18/05/1999		
I/0008	17_Change in specification of the medicinal product	07/05/1999	18/05/1999		
II/0006	Update of Summary of Product Characteristics and Package Leaflet	17/12/1998	26/04/1999	SmPC and PL	

N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/04/1999	01/07/1999	PL	
I/0004	20_Extension of shelf-life as foreseen at time of authorisation	20/11/1998	27/02/1999	SmPC	
I/0005	14_Change in specifications of active substance	27/11/1998	n/a		
I/0002	16_Change in the batch size of finished product	18/09/1997	n/a		
II/0001	New presentation(s)	18/12/1996	15/04/1997	SmPC, Labelling and PL	