Temodal

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0093	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	18/06/2021		SmPC 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).

PSUSA/2886/ 202007	Periodic Safety Update EU Single assessment - temozolomide	11/03/2021	n/a		PRAC Recommendation - maintenance
IA/0092	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	16/12/2020	n/a		
IB/0089	B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	09/10/2020	n/a		
IB/0090	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/09/2020	16/11/2020	SmPC, Labelling and PL	
IA/0088/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	09/07/2020	n/a		

IB/0087	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/10/2019	16/11/2020	SmPC, Annex II and PL	
IA/0086	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	05/09/2019	n/a		
IAIN/0085	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	12/12/2018	n/a		
T/0083	Transfer of Marketing Authorisation	17/07/2018	23/08/2018	SmPC, Labelling and PL	
IA/0084	A.7 - Administrative change - Deletion of manufacturing sites	17/08/2018	n/a		
PSUSA/2886/201707	Periodic Safety Update EU Single assessment - temozolomide	22/02/2018	28/05/2018	SmPC and PL	Please refer to Temodal-PSUSA-2886-201707 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IB/0081/G	This was an application for a group of variations. 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.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	07/02/2018	n/a		

	material/intermediate				
N/0082	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/02/2018	28/05/2018	Labelling	
IA/0079	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	15/09/2017	n/a		
IAIN/0078	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/06/2017	28/05/2018	SmPC and PL	
IA/0077	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	24/10/2016	n/a		
IA/0076/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - 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	13/05/2016	n/a		
II/0075	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/04/2016	n/a		

PSUSA/2886/201407	Periodic Safety Update EU Single assessment - temozolomide	26/03/2015	27/05/2015	SmPC and PL	Please refer to Temodal PSUSA-2886-201407 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
II/0072	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	23/04/2015	n/a		
II/0074	Submission of the final study report (plus protocol) of study RTOG-9813 by 31.12.2014 [PAC no. PAM031.1] a comparative Phase III study in first line treatment of Anaplastic Astrocytoma with concomitant radiation in order to fulfill the pending post-authorisation commitment (PAC no. PAM031.1). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		
IA/0071/G	This was an application for a group of variations. 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 B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	28/10/2014	n/a		

N/0070	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/08/2014	27/05/2015	PL	
IA/0069/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	19/06/2014	n/a		

	Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				

II/0068	Update of section 4.8 of the SmPC in order to include the calculated frequency of hepatic-related disorders. The Package Leaflet was updated accordingly. In addition, the MAH proposed changes to the minimum particulars to appear on small immediate packaging and to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	27/05/2015	SmPC, Labelling and PL	Section 4.8 of the SmPC and the Package Leaflet have been updated to include the calculated frequency of hepatic-related disorders based on clinical trial experience: Cases of elevations of liver enzymes have been commonly reported (may affect up to 1 in 10 people); Cases of hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure have been uncommonly reported (may affect up to 1 in 100 people).
II/0063	Update of sections 4.4 and 4.8 of the SmPC to include the risk of hepatic failure further to the PRAC recommendation as requested in LEG 037. The Package Leaflet was updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. Minor changes were also proposed to the labelling. 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	21/11/2013	18/12/2013	SmPC, Annex II, Labelling and PL	Further to PRAC request, the MAH conducted a cumulative review of cases of hepatic failure and related terms with temozolomide. The review identified 38 cases including fatal outcomes. The CHMP identified 6 additional cases from the literature. Liver toxicity may occur several weeks or more after the last treatment with temozolomide. As a consequence, it is recommended that baseline liver function tests should be performed prior to treatment initiation. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle and for all patients, liver function tests should be checked after each treatment cycle. Sections 4.4 and 4.8 of the SmPC have been updated.
IA/0067	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)	28/11/2013	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		
IB/0065	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	23/08/2013	n/a		
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/07/2013	18/12/2013	PL	
II/0062	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information with reported cases of fatal respiratory failure and to include pulmonary fibrosis as an adverse drug reaction further to the CHMP request following the assessment of the PSUR 13 (period 13/07/2008 to 12/07/2011). In addition, the MAH took the opportunity to introduce editorial changes in the Package Leaflet and to update the list of local representatives. Furthermore, the PI is being brought in line with the latest QRD template version 8.2. C.I.3.z - 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 - Other variation	13/12/2012	18/12/2013	SmPC, Annex II, Labelling and PL	Following the assessment of PSUR 13 (covering the period 13/07/2008 to 12/07/2011), the CHMP requested the MAH to submit a variation to update section 4.8 of the SmPC. The MAH agreed to include pulmonary fibrosis as an adverse drug reaction. However, the MAH submitted a justification for not updating the SmPC to include respiratory failure providing additional information. The CHMP did not agree with the MAH´s justification since available information indicates a causal role of temozolomide for the development of respiratory failure and its associated risk of fatality. Therefore, an update of the SmPC with this information was requested (section 4.4 and 4.8).

A20/0060	Pursuant to Article 20 of Regulation (EC) No. 726/2004, the European Commission requested the CHMP to re-evaluate the benefit-risk balance of Temodal in light of newly available data on the deficiencies in conduct of bio-analytical studies performed by the Cetero Research facilities in Houston (Texas, USA) and to give its opinion on whether the marketing authorisation in the approved indication should be maintained, varied, suspended or revoked.	20/09/2012	26/11/2012		Please refer to the assessment report: EMEA/H/C/000229/A-20/0060.
IG/0184	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/08/2012	n/a		
II/0059	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning regarding the risk of myelosuppression including prolonged pancytopenia which may in some cases result in a fatal outcome further to the CHMP request following the assessment of PSUR 13. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.0 rev. 1. Finally, changes were made to the vial label to improve the readability. C.I.3.b - Implementation of change(s) requested	24/05/2012	27/06/2012	SmPC, Annex II, Labelling and PL	In the 13th PSUR covering the period 13 July 2008 to 11 July 2011, a total of 21 fatal cases were reported in the SOC Blood and Lymphatic System Disorders. The majority of the cases discussed were related to myelosuppression with bone marrow failure, pancytopenia, neutropenia, febrile neutropenia or aplastic anaemia. As a consequence, the CHMP requested the MAH to include a warning in section 4.4 of the SmPC. Section 4.8 of the SmPC was also updated to include the risk of fatal outcome related to prolonged pancytopenia.

	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				
T/0058	Transfer of Marketing Authorisation	16/12/2011	31/01/2012		Transfer of the Marketing Authorisation Holder from Schering-Plough Europe to Merck Sharp & Dohme Limited.
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	
IA/0057	A.1 - Administrative change - Change in the name and/or address of the MAH	15/11/2011	13/01/2012	SmPC, Labelling and PL	
IB/0055/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a	10/11/2011	n/a		

	manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products A.7 - Administrative change - Deletion of manufacturing sites				
N/0056	The MAH applied to amend section 6 of the Package Leaflet with updated contact details for local representatives in Belgium, Estonia, Finland, France, Germany, Hungary, Ireland, Island, Latvia, Lithuania, Luxembourg, Malta, Portugal, Romania and United Kingdom. Furthermore, some minor linguistic corrections were introduced in French Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/09/2011	13/01/2012	PL	
N/0054	The MAH applied to update the contact details for local representatives in Belgium, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Latvia, Luxembourg, Norway, Poland, Romania, Slovakia, Slovenia and United Kingdom. Additionally, the list of the local representatives of the French Product Information has been aligned with the corresponding English annex. Finally, minor linguistic amendments have been introduced in Hungarian product leaflet. Minor change in labelling or package leaflet not	05/08/2011	13/01/2012	PL	

	connected with the SPC (Art. 61.3 Notification)				
II/0052	This type II variation concerns an update of section 4.8 of the SmPC to include information on possible risk of hepatotoxicity associated with Temodal identified following a cumulative review. The PL has been updated accordingly. In addition, the MAH took the opportunity of this variation to update the product information in line with the latest version of the QRD template (version 7.3.1), to remove the version number of the DDPS in Annex II, to use the short standard term "powder for infusion" in the small immediate packaging material and to introduce editorial changes. Furthermore, the MAH updated the list of local representatives in the PL. The PLs for hard capsules sachet and bottles was also combined in one. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	14/06/2011	SmPC, Annex II, Labelling and PL	Following a cumulative search of the Schering-Plough Global Pharmacovigilance database for hepatotoxicity related cases that occurred in patients taking temozolomide (TMZ) from 9 June 2007 to 12 July 2010 a total of eight cases were identified. Based on the evaluation of this search and on the review of the most recent post-marketing data, in addition to the previously completed assessments, a possible association between TMZ therapy and hepatotoxicity cannot be ruled out. The section 4.8 of the SmPC was updated to reflect the information on possible risk of hepatotoxicity. The PL has been updated accordingly.
IB/0053/G	This was an application for a group of variations. B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data) B.IV.z - Quality change - Change in Medical Devices - Other variation	27/05/2011	n/a	SmPC and PL	
IA/0051/G	This was an application for a group of variations.	15/12/2010	n/a		

	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) 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 B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer				
N/0050	The Marketing Authorisation Holder has applied to correct the discrepancy between the Package Leaflet approved as part of the Commission Decision and the one distributed on the market hence having three combined Package Leaflets for the three presentations. Furthermore, the details of the local representatives in Finland, Spain, Sweden and The Netherlands have also been updated. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/10/2010	n/a	PL	
IB/0049	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale	08/07/2010	n/a	SmPC	To extend the shelf-life of temozolomide powder for solution for infusion 2.5 mg/ml (EU/1/98/096/023) from 36

	(supported by real time data)				to 48 months when stored at 2°-8°C.
II/0045	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. A minor QRD related change was also introduced in Annex II. 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 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. The CHMP considers that the Pharmacovigilance System as described by the MAH is acceptable.
IB/0048	IB_33_Minor change in the manufacture of the finished product	12/11/2009	n/a		
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/10/2009	n/a	PL	
IB/0046	IB_38_c_Change in test procedure of finished product - other changes	02/10/2009	n/a		
IB/0044	Addition of two new presentations of 5 and 20 capsules for the 5 mg strength, packaged in PET/alu/PET sachets. Also, the opportunity is taken to update the contact information of a local representative in the PL. IB_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	23/06/2009	23/06/2009	SmPC, Labelling and PL	
IB/0042	IB_33_Minor change in the manufacture of the finished product	04/03/2009	n/a		

X/0035	Annex I_2.(d) Change or addition of a new pharmaceutical form	20/11/2008	17/02/2009	SmPC, Labelling and PL	
II/0039	Update of or change(s) to the pharmaceutical documentation	20/11/2008	22/01/2009	SmPC, Labelling and PL	
R/0040	Renewal of the marketing authorisation.	23/10/2008	17/12/2008	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 Temodal continues to be favourable. The renewal can be granted with unlimited validity.
II/0041	Following the assessment of the 11th PSUR, the CHMP requested the MAH to provide a complete safety review of all reported cases of interstitial pneumonitis/pneumonitis and related disorders. Based on this review, an update of section 4.8 of the SPC is proposed to include reported cases of interstitial pneumonitis/pneumonitis. Other minor SPC changes were introduced in accordance to the latest QRD template. The Package leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	23/10/2008	25/11/2008	SmPC and PL	Following the assessment of the 11th PSUR, the CHMP requested the MAH to provide a complete safety review of all reported cases of interstitial pneumonitis/pneumonitis and related disorders. Based on this review, an update of section 4.8 of the SPC is proposed to include reported cases of interstitial pneumonitis/pneumonitis. Other minor SPC changes were introduced in accordance to the latest QRD template. The Package leaflet is updated accordingly.

II/0036	Update of section 4.4 of the SPC to add information on cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, following the conclusions of the assessment of the 11th PSUR. The Package Leaflet has been updated accordingly. In addition, updates of the contact details of the local representatives in Romania and Sweden have been implemented in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	25/06/2008	SmPC and PL	The Summary of Product Characteristics is updated to include the following text - as recommended after the assessment of the 11th European Periodic Safety Update Report: "Very rare cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been observed." Accordingly in the Package Leaflet - under "Take special care with Temodal" the sentence: - "you may have a small risk of other changes in blood cells, including leukaemia." is added. In addition, updates of the contact details of the local representatives in Romania and Sweden have been implemented in the Package Leaflet.
IB/0038	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	12/06/2008	n/a	SmPC	
IA/0037	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/03/2008	n/a		
IA/0034	IA_05_Change in the name and/or address of a manufacturer of the finished product	31/08/2007	n/a		
II/0032	Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	25/07/2007	SmPC, Annex II and PL	Addition of a warning regarding the male fertility and a precaution wording regarding contraception for male patients in section 4.6 "Pregnancy and lactation" of the SPC as requested by the CHMP folliwng the assessment of the 10th PSUR. In addition, Section 4.8 of the SPC "Undesirable Effects" table 5 was updated to add the grade of thrombocytopenia. Additional editorial changes were made. The relevant sections in the Package leaflet have also been

					updated accordingly. The contact details for the local representatives of Netherlands and Norway were updated in the Package Leaflet.
IA/0033	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	04/05/2007	n/a		
X/0030	Annex I_2.(c) Change or addition of a new strength/potency	22/02/2007	23/04/2007	SmPC, Labelling and PL	
II/0031	Update of Summary of Product Characteristics, Labelling and Package Leaflet	16/11/2006	04/01/2007	SmPC, Annex II, Labelling and PL	Update of section 4.8 of the SPC to provide safety information to the physicians on gender differences in hematologic parameters occurring during the first cycle of treatment in patients receiving Temodal, and to add toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). The Package Leaflet is updated accordingly. The product information has also been updated to comply with the latest QRD templates. In addition the contact details of the Danish and Lithuanian local representatives are updated and the local representatives for Bulgaria and Romania are now listed in the Package Leaflet.
IA/0029	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	13/06/2006	n/a		
IB/0026	IB_34_b_01_Change in colour/flavour - Increase or addition: colouring system	09/06/2006	n/a	SmPC and PL	
IA/0028	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	23/05/2006	n/a		

IA/0027	IA_25_b_02_Change to comply with Ph. - compliance with EU Ph. update - excipient	16/05/2006	n/a		
IA/0025	IA_39_Change/addition of imprints, bossing or other markings	16/05/2006	n/a	SmPC and PL	
II/0024	Update of Summary of Product Characteristics and Package Leaflet	13/10/2005	15/11/2005	SmPC and PL	Update of the SPC in section 4.4 to add information on Pneumonocystiis Carinii Pneumonia and in section 4.8 to include "aplastic anaemia". The PL is updated accordingly and was also corrected to clarify the dosage schedule.
IA/0023	IA_09_Deletion of manufacturing site	11/08/2005	n/a		
IA/0022	IA_09_Deletion of manufacturing site	11/08/2005	n/a		
II/0021	The MAH applied for an additional indication in the treatment of newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment. In addition, minor editorial changes have been made in the Labelling and corresponding changes have been introduced in the Package Leaflet. Extension of Indication	21/04/2005	03/06/2005	SmPC, Labelling and PL	*Please refer to module 6 for Scientific Discussion
IB/0020	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	06/09/2004	n/a		
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/05/2004	n/a	PL	

R/0013	Renewal of the marketing authorisation.	20/11/2003	10/03/2004	Annex II and Labelling	
II/0014	Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	05/02/2004	SmPC and PL	
IA/0018	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	23/01/2004	n/a		
IA/0017	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	23/01/2004	n/a		
IA/0016	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	23/01/2004	n/a		
IA/0015	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	09/12/2003	n/a		
I/0011	15_Minor changes in manufacture of the medicinal product	15/08/2003	21/08/2003		
II/0009	Update of Summary of Product Characteristics and Package Leaflet	21/11/2002	06/03/2003	SmPC and PL	
I/0010	Change of the manufacturing site(s) for part or all of the manufacturing process of the medicinal product. 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	17/01/2003	22/01/2003		
I/0008	15a_Change in IPCs applied during the manufacture of the product	30/08/2002	04/09/2002		

II/0007	Update of Summary of Product Characteristics and Package Leaflet	15/11/2001	11/04/2002	SmPC and PL	
II/0004	Update of or change(s) to the pharmaceutical documentation	21/03/2002	11/04/2002		
I/0006	14_Change in specifications of active substance	18/04/2001	n/a		
I/0005	24_Change in test procedure of active substance	16/03/2001	n/a		
II/0002	Extension of Indication	20/05/1999	18/08/1999	SmPC and PL	