VELCADE

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IA/0096	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	13/05/2021		SmPC and PL	
PSUSA/424/202004	Periodic Safety Update EU Single assessment - bortezomib	10/12/2020	18/02/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/424/202004.
IA/0095	B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	28/10/2020	n/a		

[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).

II/0093	Update of the RMP (finally agreed version 30.2) in line with the latest RMP template revision 2; as a consequence, Annex II of the PI is updated to reflect the removal of the additional risk minimisation activities (educational materials). In addition, the MAH took the opportunity to update the list of local representatives in the PL. Furthermore, the PI is being brought in line with the latest QRD template (version 10.1). 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	13/02/2020	18/02/2021	Annex II and PL	
PSUSA/424/201904	Periodic Safety Update EU Single assessment - bortezomib	28/11/2019	n/a		PRAC Recommendation - maintenance
IA/0091/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 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	31/05/2019	n/a		

PSUSA/424/201804	Periodic Safety Update EU Single assessment - bortezomib	13/12/2018	20/02/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/424/201804.
II/0090	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/09/2018	20/02/2019	SmPC and PL	
IB/0087	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	10/01/2018	n/a		
PSUSA/424/201704	Periodic Safety Update EU Single assessment - bortezomib	30/11/2017	n/a		PRAC Recommendation - maintenance
IA/0086	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)	05/10/2017	n/a		
IA/0084	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	24/05/2017	n/a		
IB/0083	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/02/2017	08/02/2018	SmPC, Annex II, Labelling and PL	
PSUSA/424/201604	Periodic Safety Update EU Single assessment - bortezomib	01/12/2016	n/a		PRAC Recommendation - maintenance

IAIN/0081	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	21/06/2016	n/a		
IA/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) 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	19/05/2016	n/a		
II/0079	Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to include information from paediatric study AALL07P1. The MAH also took the opportunity to correct some minor editorial mistakes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/12/2015	25/01/2016	SmPC	For transplant eligible patients, dose modification recommendations described for monotherapy should be followed (for more information, please refer to the SmPC. A Phase II, single arm activity, safety, and pharmacokinetic trial conducted by the Children's Oncology Group assessed the activity of the addition of bortezomib to multi agent re-induction chemotherapy in paediatric and young adult patients with lymphoid malignancies (pre-B cell acute lymphoblastic leukaemia [ALL] with T-cell ALL, and T-cell lymphoblastic lymphoma [LL]). An effective re-induction multi-agent chemotherapy regimen was administered in 3 blocks. VELCADE was administered only in Blocks 1 and 2 to avoid potential overlapping toxicities with coadministered drugs in Block 3.

					Complete response (CR) was evaluated at the end of Block 1. In B-ALL patients with relapse within 18 months of diagnosis (n = 27) the CR rate was 67% and the 4-month event free survival rate was 44%. In B-ALL patients with relapse 18-36 months from diagnosis (n = 33) the CR rate was 79% and the 4-month event free survival rate was 73%. The CR rate in first-relapsed T-cell ALL patients (n = 22) was 68% and the 4-month event free survival rate was 67%. The reported efficacy data are considered inconclusive. There were 140 patients with ALL or LL enrolled and evaluated for safety. No new safety concerns were observed when VELCADE was added to the standard paediatric pre B cell ALL chemotherapy backbone. The following adverse reactions (Grade ≥ 3) were observed at a higher incidence in the VELCADE containing treatment regimen as compared with a historical control study in which the backbone regimen was given alone: peripheral sensory neuropathy; ileus; hypoxia. No information on possible sequelae or rates of peripheral neuropathy resolution was available in this study. Higher incidences were also noted for infections with Grade ≥ 3 neutropenia, increased ALT, hypokalaemia and hyponatraemia. No recommendation on a posology can be made considering the currently available data.
PSUSA/424/201504	Periodic Safety Update EU Single assessment - bortezomib	19/11/2015	14/01/2016	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/424/201504.
IA/0077	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	16/07/2015	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IAIN/0076/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) B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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)	08/06/2015	n/a		
II/0075	Update of section 5.1 Pharmacodynamic properties of the SmPC following the submission of long term follow-up and survival analysis from Study Doxil-MMY-3001 - evaluation of efficacy and safety for Doxil/Caelyx in combination with VELCADE compared to the VELCADE monotherapy for treatment of subjects with multiple myeloma whose disease had progressed after an initial response to at least 1 line of prior therapy or was refractory to initial treatment. The MAH had committed to provide this information during VELCADE variation procedure EMEA/H/C/539/II/63 and CAELYX variation procedure EMEA/H/C/089/II/45. Additional editorial amendments are introduced and the contact details of local representatives are updated in the package leaflet.	23/04/2015	14/01/2016	SmPC and PL	

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0074/G	This was an application for a group of variations. 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.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	26/02/2015	n/a		
II/0072	Extension of indication for the use of VELCADE in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma. Consequently, the MAH proposed updates of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	18/12/2014	30/01/2015	SmPC and PL	Extension of indication to include the use of Velcade in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation; as a consequence, 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.
PSUV/0073	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
PSUV/0070	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance

N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/03/2014	30/01/2015	PL	
IB/0069	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	16/01/2014	n/a		
IB/0068	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	16/01/2014	n/a		
R/0066	Renewal of the marketing authorisation.	21/11/2013	10/01/2014	SmPC and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of Velcade continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Velcade, subject to the conditions and obligations as laid down in Annex II to the Opinion. The CHMP recommends that the renewal be granted with unlimited validity.
II/0063/G	This was an application for a group of variations. Extensions of indication for Velcade in combination with pegylated liposomal doxorubicin or in combination with dexamethasone in patients with relapsed and /or progressive multiple myeloma who have received at least 1 prior therapy. Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The package leaflet has been updated accordingly. Editorial changes were also made to the	21/11/2013	18/12/2013	SmPC, Annex II and PL	Please refer to Scientific Discussion Velcade-H-539-II-63G-AR.

	product information. Annex II has also been corrected to add the key elements with regards to the induction transplant regimens to minimise the risk of medication errors. The list of local representatives in the package leaflet has also been updated. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0067	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/08/2013	n/a		
II/0059	Extension of the indication of Velcade in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation. Consequently, sections 4.1, 4.2, 4.3, 4.4, 4.6, 4.8 and 5.1 of the Summary of Product Characteristics and the package leaflet have been updated. The MAH also took the opportunity to make editorial changes to the product information. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/06/2013	31/07/2013	SmPC and PL	Please refer to Scientific Discussion Velcade-H-539-II-59-AR.
II/0062	Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to add the results of a study on Velcade	27/06/2013	31/07/2013	SmPC, Annex	There are limited data concerning retreatment with VELCADE.

	retreatment in patients with relapsed multiple myeloma. The package leaflet was updated accordingly. In addition, the MAH took the opportunity to make editorial changes and to update the list of local representatives in the Package Leaflet, including the contact details of the local representatives in Croatia. Furthermore, the product information was updated in line with the latest QRD template version 9. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			II and PL	The MAH submitted the results of Study MMY 2036 (RETRIEVE), a Phase II, single arm, open label study designed to determine the efficacy and safety of retreatment with Velcade in 130 patients with multiple myeloma. Patients (≥ 18 years of age) who previously had at least partial response on a Velcade containing regimen were retreated upon progression. At least 6 months after prior therapy, Velcade was started at the last tolerated dose of 1.3 mg/m2 (n=93) or ≤ 1.0 mg/m2 (n=37) and given on days 1, 4, 8 and 11 every 3 weeks for maximum of 8 cycles either as single agent or in combination with dexamethasone in accordance with the standard of care. Dexamethasone was administered in combination with Velcade to 83 patients in Cycle 1 with an additional 11 patients receiving dexamethasone during the course of Velcade treatment. The primary endpoint was best confirmed response to retreatment as assessed by EMBT criteria. The overall best response rate (CR + PR), to retreatment in 130 patients was 38.5% (95% CI: 30.1, 47.4). The most common all grade adverse events occurring in at least 25% of patients were thrombocytopenia (55%), neuropathy (40%), anaemia (37%), diarrhoea (35%), and constipation (28%). All grade peripheral neuropathy and grade ≥ 3 peripheral neuropathy were observed in 40% and 8.5% of patients, respectively.
IA/0065/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in	16/04/2013	n/a		

	the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) 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) A.7 - Administrative change - Deletion of manufacturing sites				
II/0061	Update of section 4.4 of the SmPC to add a warning on Progressive Multifocal Leukoencephalopathy. The Package Leaflet is updated accordingly. The MAH also took the opportunity to make minor editorial changes and update the list of local representatives in the package leaflet. Furthermore, Annex II has been updated in line with the latest QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/03/2013	31/07/2013	SmPC, Annex II and PL	Section 4.4 of the SmPC has been updated in order to include a warning on Progressive Multifocal Leukoencephalopathy (PML). Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with VELCADE. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of VELCADE. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. In addition VELCADE should be discontinued if PML is diagnosed. The Package Leaflet was updated accordingly.
II/0057	Additional batch size for the finished product.	13/12/2012	13/12/2012		

	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				
II/0058/G	This was an application for a group of variations. Change in the manufacturing sites for the finished product and change to batch size of the finished product. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging 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 aseptically manufactured) excluding biological/ immunological medicinal products 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 A.7 - Administrative change - Deletion of manufacturing sites 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	20/09/2012	20/09/2012		

	manufactured by complex manufacturing processes B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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)				
X/0047	Annex I_2.(e) Change or addition of a new route of administration Annex I_2.(e) Change or addition of a new route of administration	21/06/2012	20/09/2012	SmPC, Annex II, Labelling and PL	Extension application for a new route of administration for subcutaneous use of Velcade 3.5 mg powder for solution for injection. Please refer to EPAR H-539-X-47-AR
IAIN/0060	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
A20/0056	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).	16/02/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/00539/A-20/056
II/0054	Update of section 4.8 of the SmPC in order to the adverse reactions "optic neuropathy" and "different degrees of visual impairment (up to blindness)" with a rare frequency. The Package Leaflet has been updated accordingly. In addition, editorial changes have also been made to the SmPC and Package Leaflet.	19/01/2012	21/03/2012	SmPC and PL	The MAH conducted cumulative reviews of reports of optic neuropathy and blindness in which 43 cases were identified. Among those cases, the CHMP considered 7 cases of optic neuropathy likely due to Velcade. The CHMP agreed that Velcade might increase the risk of optic neuropathy and might induce various degrees of visual impairment. The Product information has been

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				updated accordingly.
S/0052	"7th Annual Re-assessment"	15/12/2011	19/03/2012	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable. The CHMP considered that, as all Specific Obligations have been fulfilled, there are no remaining grounds for the Marketing Authorisations to remain under exceptional circumstances.
II/0053	Update of section 5.1 of the SmPC with final survival data from Study MMY-3002. The MAH also took the opportunity to make minor editorial changes to the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/12/2011	19/03/2012	SmPC	The Phase 3 Study MMY-3002 (VISTA) was an open-label multicentre randomised placebo-controlled trial to investigate the efficacy of bortezomib (Velcade) in untreated patients with a diagnosis of multiple myeloma who cannot be treated with high-dose chemotherapy/stem cell transplantation (HDC/SCT) because of age (> 65 y) or other conditions. Results from this study supported the extension of the indication of Velcade in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant (variation EMEA/H/C/539/II/0028 approved in 2008). In this variation application, the Marketing Authorisation Holder submitted the final overall survival data from Study MMY-3002. At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and

					patients in the melphalan/prednisone (M+P) arm were offered Velcade/melphalan/prednisone (Vc+M+P) treatment. Median follow-up was 16.3 months. The final survival update was performed with a median duration of follow-up of 60.1 months. A statistically significant survival benefit in favour of the Vc+M+P treatment group was observed (HR=0.695; p=0.00043) despite subsequent therapies including VELCADE-based regimens. Median survival for the Vc+M+P treatment group was 56.4 months compared to 43.1 for the M+P treatment group. Section 5.1 of the SmPC has been updated to include these final results.
II/0050	Update of section 4.5 of the Summary of Product Characteristics (SmPC) with regard to the interaction of Velcade with CYP3A4 inducers further to the results of a drug-drug interaction study of Velcade and rifampicin and dexamethasone. The Package leaflet has been updated accordingly. The MAH also took the opportunity to update the list of local representatives in the 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	21/07/2011	24/08/2011	SmPC and PL	A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. Therefore, the concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced. In the same drug-drug interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, there was no significant effect on the pharmacokinetics of bortezomib based on data from 7 patients.
IB/0051/G	This was an application for a group of variations. 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	11/08/2011	n/a		

	corresponding test method B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0048/G	This was an application for a group of variations. Addition of an alternative manufacturer of the finished product responsible for manufacturing, primary packaging and QC testing. As a result, there was a change in the batch size and other minor changes to the manufacturing process. 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.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging 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 aseptically manufactured) excluding biological/ immunological medicinal products 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	21/07/2011	21/07/2011		

	and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation				
IB/0049	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	21/07/2011	n/a		
II/0046	Update of sections 4.2, 4.3, 4.4 and 5.2 of the SmPC and the Package Leaflet (PL), in particular to remove the contraindication of Velcade in patients with severe hepatic impairment, further to the results of a study of Velcade in subjects with advanced malignancies and varying degrees of hepatic dysfunction that was conducted in order to fulfil a specific obligation (SO2 011.1). The MAH also took the opportunity to make editorial changes to the product information and update the list of local representatives in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	29/06/2011	SmPC and PL	At the time of the initial Marketing authorisation application, bortezomib was not formally studied in patients with impaired hepatic function. Therefore, further to the lack of data in this special population a contraindication in patients with severe hepatic impairment and the applicant committed to conduct a pharmacokinetic study of Velcade in patients with hepatic impairment (Specific obligation SOB 011). In this variation application, the MAH provided the results of a phase 1 pharmacokinetic study of Velcade in patients with advanced malignancies and varying degrees of liver dysfunction. The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in this during the first treatment cycle, including 61 patients primarily with solid tumors and varying degrees of hepatic impairment at bortezomib doses ranging from 0.5 to 1.3 mg/m2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment.

					Further to these results, the contraindication in patients with severe hepatic impairment has been removed. Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be closely monitored. Sections 4.2, 4.3, 4.4 and 5.2 of the SmPC and the Package Leaflet have been amended accordingly.
S/0045	Annual re-assessment.	23/09/2010	13/12/2010	SmPC, Annex II, Labelling and PL	6th annual re-assessment The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
II/0041	Further to the results of a phase 1/2 study conducted as a specific obligation (SOB 015) to determine the safety and efficacy of VELCADE in patients with previously treated light-chain amyloidosis, the marketing authorisation holder of VELCADE applied to update section 4.4 of the Summary of Product Characteristics (SmPC) to remove the warning on amyloidosis and to include the results of this study in section 5.1 of the SmPC. The package leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/05/2010	02/07/2010	SmPC, Annex II and PL	At the time of the initial Marketing authorisation application, the applicant committed to present the results from the planned Phase I/II clinical trial aimed at ruling out the possibility that secondary to proteasome inhibition bortezomib treatment may increase the risk of amyloidosis and/or may have an adverse impact on its progression and organ manifestations (Specific obligation SOB 015). Study CAN-2007 was a Phase 1/2, open-label, dose-escalation study investigating single-agent therapy with VELCADE in subjects with previously treated AL amyloidosis who required further treatment. The primary objective of the Phase 1 portion of the study was to determine the Maximal Tolerated Dose (MTD)

					based on Dose Limiting Toxicity (DLT) of single agent therapy with VELCADE in subjects with previously treated AL-amyloidosis who required further therapy and the primary objective of the Phase 2 portion of the study was to determine the safety of VELCADE in this patient population. The secondary objective of the Phase 2 portion of the study was to determine the haematologic response rate (CR+PR) and duration of response at the MTD (or maximum allowed doses if MTD was not reached). The safety profile of VELCADE emerging from study CAN-2007 is consistent with the current overall knowledge of VELCADE safety. Comparison of CAN-2007 safety findings with those of the larger APEX study in multiple myeloma patients shows remarkably similar patterns. No unexpected AE was recorded. It is highly relevant that VELCADE treatments do not appear to worsen organ damage and/or clinical outcome of the underlying AL-amyloidosis. As a consequence, the warning on section 4.4 of the SmPC has been removed. Furthermore, the results of this study have been included in section 5.1 of the SmPC to indicate that no new safety concerns were observed during the study, and in particular VELCADE did not exacerbate target organ damage (heart, kidney and liver). In an exploratory efficacy analysis
IA/0044	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished	22/06/2010	n/a		

	product, including quality control sites (excluding manufacturer for batch release)				
II/0040	Update of section 5.1 of the Summary of Product Characteristics with updated survival data from Study MMY-3002. The MAH also took the opportunity to include a correction and update the list of local representatives in the 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	22/04/2010	02/06/2010	SmPC and PL	The Phase 3 Study MMY-3002 (VISTA) was an open-label multicentric randomized placebo-controlled trial to investigate the efficacy of bortezomib (Velcade) in untreated patients with a diagnosis of multiple myeloma who cannot be treated with high-dose chemotherapy/stem cell transplantation (HDC/SCT) because of age (> 65 y) or other conditions. Results from this study supported the extension of the indication of Velcade in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant (variation EMEA/H/C/539/II/0028 approved in 2008). In this variation application, the Marketing Authorisation Holder submitted updated survival data from Study MMY-3002. This survival update was performed with a median duration of follow-up of 36.7 months. A statistically significant survival benefit in favour of the Vc+M+P treatment group was observed (HR=0.65; p=0.00084), despite subsequent therapies including VELCADE-based regimens. While the median survival in M+P treatment group has now been estimated at 43.1 months, the median survival on the Vc+M+P treatment group has not been reached.
IB/0042	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/05/2010	n/a	SmPC, Annex II and PL	Update of sections 2, 4.2, 4.6, 5.1, 6.5 and 10 of the Summary of Product Characteristics, Annex II and the

					Package Leaflet, to align with the new QRD template version 7.3.
II/0039	Further to the conduct of cumulative reviews requested by the CHMP in the assessment of the 10th PSUR and 5th annual re-assessment, the MAH proposed to update section 4.4 of the Summary of Product Characteristics (SmPC) to add a warning on Reversible Posterior Leukoencephalopathy Syndrome (RPLS) and to add the adverse reactions in section 4.8 RPLS, acute febrile neutrophilic dermatosis and leukocytoclastic vasculitis. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	27/04/2010	SmPC and PL	Further to the assessment of the 10th PSUR (covering the period from 26 October 2008 to 25 April 2009), the Marketing Authorisation Holder (MAH) was requested by the CHMP to conduct a cumulative review of reports of reversible posterior leukoencephalopathy syndrome (RPLS), leukocytoclastic vasculitis (LCV), and acute febrile neutrophilic dermatosis (AFND). The cumulative review of currently available safety data from clinical trials, literature, and post-marketing adverse event reports shows that RPLS is an ADR associated with the use of Velcade. As a consequence, the product information was updated to include in section 4.4 of the SPC that: "There have been reports of RPLS in patients receiving VELCADE. RPLS is a rare, reversible, rapidly evolving neurological condition, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing RPLS, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing RPLS is not known." RPLS was also added in section 4.8 of the SmPC as an adverse reaction from post-marketing experience with a frequency "not known".

					As a consequence of the cumulative review on leukocytoclastic vasculitis, section 4.8 of the SPC has been amended to indicate that "vasculitic rash (including leukocytoclastic vasculitis)" is an adverse reaction from post-marketing experience with a frequency "not known". Further to the conduct of the cumulative review, it was also considered that there is sufficient evidence to support that Acute febrile neutrophilic dermatosis is an adverse drug reaction associated with the use of Velcade and was consequently added in section 4.8 of the SmPC as an adverse reaction from post-marketing experience with a frequency "not known". The Package leaflet has been updated accordingly.
S/0035	Annual re-assessment.	24/09/2009	30/11/2009	SmPC and Annex II	5th annual re-assessment The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that amendment to Annex I of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances. Annex II has been amended according to the conclusions reached during the CHMP discussion.
II/0036	Update of Summary of Product Characteristics Update of section 5.1 of the Summary of Product	24/09/2009	28/10/2009	SmPC	There is a body of preclinical studies and clinical observations on the effect of Velcade on bone. As a consequence, the following paragraph was added to

	Characteristics (SPC) to reflect the effects of Velcade on bone further to data from in vitro, ex-vivo in animal models and in patients treated with bortezomib. The Marketing Authorisation Holder also took the opportunity to include the date of the latest renewal in section 9 of the SPC. Update of Summary of Product Characteristics				section 5.1 of the Summary of Product Characteristics (SPC): "Data from in vitro, ex-vivo, and animal models with Bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with Bortezomib."
IB/0038	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	18/09/2009	n/a		
IB/0037	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	18/09/2009	n/a		
II/0033	The Marketing Authorisation Holder applied for the addition of an alternative finished product manufacturer, primary packaging and QP release-testing site for Velcade 3.5 mg powder and consequentially, minor changes to the manufacturing process, in-process controls and vials. Quality changes	25/06/2009	30/06/2009		
II/0034	Update of section 4.8 of the SPC to include a recommendation regarding the use of antiviral prophylaxis therapy for herpes zoster virus reactivation in patients treated with Velcade and to add Steven Johnson Syndrome and Toxic Epidermal Necrolysis as adverse reactions from post-marketing reports with a frequency "not known", further to	23/04/2009	29/05/2009	SmPC and PL	Based on the cumulative review of available safety data, patients receiving VELCADE may be at an increased risk for developing herpes zoster reactivation. Additionally, several well-controlled studies have shown significant reductions in the incidence of herpes zoster among patients receiving antiviral prophylaxis. Therefore, the CHMP agreed on changes to section 4.8 of the SPC as

	safety related revisions to the Company Core Data Sheet (CCDS). The Package Leaflet is updated accordingly. The MAH also took the opportunity to make some editorial changes to the SPC and to update the contact details of Bulgaria and Germany in the list of local representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet				follows: "Herpes zoster virus reactivation Antiviral prophylaxis should be considered in patients being treated with VELCADE. In the Phase III study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with Vc+M+P compared with M+P (14% vs 4% respectively). Antiviral prophylaxis was administered to 26% of the patients in the Vc+M+P arm. The incidence of herpes zoster among patients in the Vc+M+P treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis." In addition, further to a cumulative review of the safety data, "Steven Johnson Syndrome" and "Toxic Epidermal Necrolysis" were added to section 4.8 of the SPC and to the Package Leaflet as adverse reactions from post-marketing reports with a frequency "not known"
R/0032	Renewal of the marketing authorisation.	22/01/2009	31/03/2009	SmPC, Annex II, Labelling and PL	
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/11/2008	n/a	Labelling	
S/0030	Annual re-assessment.	25/09/2008	04/11/2008	Annex II	4th Annual Reassessment The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment to Annexes I, and III

					of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances.
II/0028	Extension of Indication	24/07/2008	29/08/2008	SmPC, Annex II and PL	Extension of the indication for Velcade in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant. Subsequently, changes to sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SPC have been made. The Package Leaflet has been updated accordingly. Annex II has been updated to include the agreed version of the EU RMP (version 2.0). Please refer to Scientific Discussion Velcade-H-C-539-II-28.
II/0029	Update of SPC sections 4.2, 4.4 & 5.2 based on available data from a renal impairment study, a specific obligation to the original marketing authorisation. Further, as requested with the CHMP assessment of PSUR 7, SPC section 4.8 was updated with the ADR"septic shock" under the SOC Infections and infestations in the Post Marketing Experience paragraph. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	29/07/2008	SmPC and PL	In the renal impairment study patients were enrolled with various degrees of renal impairment. Exposure to Velcade (dose-normalized AUC and Cmax) was comparable among all the groups. In patients with renal impairment (CCL > 20 ml/min/1.73m2) the pharmacokinetics of Velcade are not influenced and therefore, dosing adjustments are not necessary. However, the available data are very limited to demonstrate that Velcade total body clearance is not modified when the medicinal product is administered at therapeutic doses to patients with creatinine clearance below 20 mL/min/1.73 m2 not undergoing dialysis.
II/0027	Addition of a contraindication in Acute diffuse infiltrative pulmonary and pericardial disease.	19/03/2008	21/04/2008	SmPC and PL	Following the review of a Follow-up measure, the CHMP requested that the product information for Velcade should be amended to add a contraindication in acute

	Update of Summary of Product Characteristics and Package Leaflet				diffuse infiltrative pulmonary and pericardial disease in section 4.3 of the SPC. In addition, the current warning on pulmonary disorders in section 4.4 has been updated and cardiac and respiratory adverse events based on the post-marketing experience have been added to section 4.8 of the SPC. The package leaflet has been updated accordingly. Based on the reviewed data, the CHMP considered that the observed pulmonary drug-induced disease confirmed that the benefit of Velcade in patients with acute diffuse infiltrative pulmonary disease did not outweigh the risk. The contraindication in patients with ADIPD represents the best way to prevent adverse and fatal events. Furthermore, it was agreed to amend the current warning on pulmonary disorders in section 4.4 of the SPC to provide recommendation on the treatment and clinical actions to be put in place. In addition, based on the review of cardiac disorders and serious adverse events associated with fluid retention, the CHMP considered that Velcade should be contraindicated in patients with pericardial disease. Section 4.8 of the SPC has also been updated with a number of cardiac and respiratory, thoracic and mediastinal adverse events based on the post-marketing experience. The package leaflet has been updated accordingly.
II/0026	New presentation	19/03/2008	21/04/2008	SmPC,	

	New presentation(s)			Labelling and PL	
II/0024	Change to the specifications for the finished product. Change(s) to the test method(s) and/or specifications for the finished product	21/02/2008	28/02/2008		
II/0023	Change to the specifications for the active substance. Change(s) to the test method(s) and/or specifications for the active substance	21/02/2008	28/02/2008		
S/0022	Annual re-assessment.	15/11/2007	10/01/2008	Annex II	3rd Annual Reassessment The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of Annexes I and III of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances.
II/0025	Update of Summary of Product Characteristics	15/11/2007	14/12/2007	SmPC	This variation concerns an update of section 4.5 of the SPC with the results of two drug interaction studies with a CYP3A4 inhibitor and a CYP2C19 inhibitor, respectively, and was submitted by the MAH upon request by the CHMP following the assessment of Specific obligations 012 and 013. The SPC has been updated with the following information: A drug-drug interaction study based on data from 12 patients, assessing the effect of ketoconazole, a potent CYP3A-inhibitor, showed a bortezomib AUC mean

					increase of 35% (CI90% [1.032 to 1.772]). Therefore patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). In a drug-drug interaction study based on data from 17 patients, assessing the effect of omeprazole, a potent CYP2C19-inhibitor, there was no significant effect on the pharmacokinetics of bortezomib. Patients should be closely monitored when given bortezomib in combination with CYP2C19-inhibitors (e.g. fluoxetine). In the absence of drug-drug interaction studies investigating the effect of CYP3A4-inducers on the PK of bortezomib, patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inducers (e.g. rifampicin).
II/0021	Change(s) to the manufacturing process for the active substance	20/09/2007	26/09/2007		
II/0019	Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/05/2007	30/07/2007	SmPC, Labelling and PL	The MAH applied for a type II variation to update sections 4.2 and 4.4 of the SPC with more information regarding 'motor neuropathy'. The CHMP considered that in order to try to identify patients at risk of neuropathy, a diagnostic approach that would include a neurological assessment seems to be necessary, especially in those patients experiencing new or worsening peripheral neuropathy. Further, section 4.4 of the SPC has been updated with information regarding a potential interaction with cytarabine. In a clinical trial, two patients given high-dose cytarabine (2 g/m2 per day) by continuous

					infusion over 24 hours with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2g/m2 per day) by continuous infusion over 24 hours is not recommended. Section 4.8 of the SPC has been updated with reference ot the ADRs 'hepes zoster (including disseminated)', 'ophthalmic herpes', 'herpes meningoencephalitis', 'autonomic neuropathy' and 'angiooedema'. Further, section 5.2 of the SPC has been updated with the results of Study M34103-058 on clinical pharmacokinetics as follows: "Following intravenous bolus administration of a 1.0 mg/m2 and 1.3 mg/m2 dose to eleven patients with multiple myeloma and creatinine clearance values greater than 50 ml/min, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/ml, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/ml for the 1.0 mg/m2 dose and 89 to 120 ng/ml for the 1.3 mg/m2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 l/h following the first dose for doses of 1.0 mg/m2 and 1.3 mg/m2, respectively, and ranged f
IB/0020	IB_42_a_01_Change in shelf-life of finished product -	28/03/2007	n/a	SmPC	

	as packaged for sale				
S/0016	Annual re-assessment.	18/10/2006	03/01/2007	SmPC, Annex II, Labelling and PL	2nd Annual Reassessment: The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, recommended that amendments of Annexes I, II, IIIA and IIIB of the Commission Decision, in line with the latest QRD templates, are necessary and that the marketing authorisation remains under exceptional circumstances.
IB/0018	IB_33_Minor change in the manufacture of the finished product	30/11/2006	n/a		
IA/0017	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	10/11/2006	n/a		
II/0015	Update of Summary of Product Characteristics and Package Leaflet	28/06/2006	28/07/2006	SmPC and PL	The MAH applied for a type II variation, upon request by CHMP, to include further pulmonary safety information in section 4.4 of the Summary of Product Characteristics (SPC) and to update section 4.8 of the SPC with the following ADRs: "pneumonitis", "interstitial pneumonia", "Acute Respiratory Distress Syndrome (ARDS)", "encephalopathy", "cardiac tamponade", "ischemic colitis" and "liver failure". In addition, the MAH took the opportunity to update the addresses of the local representatives in the Package Leaflet. With reference to pulmonary disorders, there have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis,

					interstitial pneumonia, lung infiltration, and Acute Respiratory Distress Syndrome (ARDS) in patients receiving VELCADE. Some of these events have been fatal. A higher proportion of these events has been reported in Japan. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed and patients treated appropriately.
S/0011	Annual re-assessment.	13/10/2005	19/01/2006	Annex II	1st Annual Reassessment: The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of Annexes I and III of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances. Annex II has been amended according to the conclusions reached during the CHMP discussion
II/0014	Update of Summary of Product Characteristics	15/09/2005	19/10/2005	SmPC	The MAH applied for an update of sections 4.4 and 4.8 of the SPC to include additional information regarding hepatic and cardiac adverse events resulting from ongoing safety monitoring. A warning on "Hepatic Reactions" was added: "Rare cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include asymptomatic increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib." The ADR "uncommon hyperbilirubinaemia" was added to Hepatobiliary disorders and "rare liver failure" to post-

					marketing experience information in section 4.8. Further, the warning in section 4.4 on "Heart failure" was amended and now reads: "Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. In a phase III randomized, comparative study the incidence of heart failure in the VELCADE group was similar to that in the dexamethasone group. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored." Finally, the ADR "Rare new onset of decreased left ventricular ejection fraction" was added to cardiac disorders in Section 4.8.
II/0009	Change(s) to the test method(s) and/or specifications for the active substance	15/09/2005	19/09/2005		
IB/0012	IB_17_a_Change in re-test period of the active substance	07/09/2005	n/a		
II/0010	Change(s) to the test method(s) and/or specifications for the finished product	27/07/2005	02/08/2005		
II/0008	Update of Summary of Product Characteristics	23/06/2005	27/07/2005	SmPC	The MAH applied for an update of SPC section 4.9 "Overdosage" to include additional information following the assessment of the first PSUR and further to new non-clinical data on an investigational model (in vitro and in vivo), which are relevant to the clinical overdose situation. In line with the current Guideline on SPCs, references to the animal models have been included in SPC section 5.3.

					Two cardiovascular safety pharmacology studies in monkeys and dogs show that IV doses approximately two to three times the recommended clinical dose on a mg/m2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. In dogs the decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. Moreover, in dog studies, an increase in the corrected QT interval was observed. In patients, overdosage more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. There is no known specific antidote for VELCADE overdosage. In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature.
II/0007	Update of Summary of Product Characteristics and Package Leaflet	23/06/2005	27/07/2005	SmPC and PL	The MAH applied for an update of SPC section 4.8 "Undesirable effects" to include additional information regarding adverse reactions (cardiac tamponade, ischemic colitis, encephalopathy) further to the assessment of the first PSUR. In addition, acute pancreatitis and a wording on ECG investigations were included in section 4.8. The MAH also took this opportunity to re-organise the information in section 4.8 in accordance with the SPC guideline. In addition, the list of local representatives in the Patient Leaflet was updated.

IA/0013	IA_28_Change in any part of primary packaging material not in contact with finished product	22/07/2005	n/a		
II/0005	Extension of Indication	16/03/2005	20/04/2005	SmPC, Labelling and PL	Extension of the indication to allow patients who have received at least one prior therapy (instead of at least two) to be treated. As a result, sections 4.1, 4.2, 4.4, 4.8 and 5.1 in the SPC have been amended and corresponding changes in the PL have been made. Please refer to the Scientific Discussion Velcade-H-539-II-05.
IB/0006	IB_42_a_03_Change in shelf-life of finished product - after dilution/reconstitution	08/11/2004	n/a	SmPC and PL	
T/0004	Transfer of Marketing Authorisation	30/07/2004	20/09/2004	SmPC, Annex II, Labelling and PL	Transfer of the Marketing Authorisation from Millenium Pharmaceuticals, Ltd.to Janssen-Cilag International NV.
IA/0002	IA_13_a_Change in test proc. for active substance - minor change IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	10/05/2004	n/a		
IA/0001	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	10/05/2004	n/a	PL	