



Tysabri

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
T/0110	Transfer of Marketing Authorisation	03/07/2018	02/08/2018	SmPC, Labelling and PL	
IB/0108	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/04/2018	02/08/2018	Labelling	
IA/0109	A.7 - Administrative change - Deletion of manufacturing sites	26/03/2018	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).



PSUSA/2127/ 201708	Periodic Safety Update EU Single assessment - natalizumab	08/03/2018	n/a		PRAC Recommendation - maintenance
IB/0107/G	This was an application for a group of variations. B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line) B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	18/12/2017	n/a		
II/0101	Submission of the final clinical study report for TYGRIS, a post-marketing safety observational cohort program designed to obtain long-term safety data (approximately 5 years) in subjects with MS treated with natalizumab, and comprising parallel studies 101MS402 (United States and Canada) and 101MS403 (Rest of World). An updated RMP version 23 was agreed during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/07/2017	n/a		n/a
IB/0105	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/06/2017	n/a		

II/0102	<p>Submission of the final clinical study report for study STRATIFY-2 (101JC402), an observational, longitudinal cohort study designed to gather post-marketing data on the incidence of progressive multifocal leukoencephalopathy (PML) in natalizumab-treated subjects with MS. An updated RMP version 23 was provided accordingly.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>	06/04/2017	n/a		N/A
IA/0104	A.7 - Administrative change - Deletion of manufacturing sites	05/04/2017	n/a		
PSUSA/2127/201608	Periodic Safety Update EU Single assessment - natalizumab	09/03/2017	n/a		PRAC Recommendation - maintenance
IG/0709	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	27/02/2017	n/a		
II/0095	<p>Update of section sections 4.2, 4.3, 4.8, 5.1 and 5.2 of the SmPC based on the results of paediatric studies 101MS028 and 101MS328, in accordance with paediatric investigation plan (EMA-001095-PIP-12). The Package Leaflet has been updated accordingly. The MAH also took the opportunity to make minor amendments in the SmPC and to update the contact details of the local representative in Denmark in the Package Leaflet. An updated RMP version 21 was agreed as part of the procedure.</p>	23/02/2017	11/09/2017	SmPC	<p>The safety and efficacy of TYSABRI in children and adolescents up to 18 years have not been established. No recommendation on a posology can therefore be made. A post-marketing meta-analysis was conducted using data from 621 paediatric MS patients treated with TYSABRI (median age 17 years, range was 7-18 years, 91% aged ≥14 years). Within this analysis, a limited subset of patients with data available prior to treatment (158 of the 621 patients) demonstrated a reduction in ARR from 1.466 (95% CI 1.337, 1.604) prior to treatment to 0.110 (95% CI 0.094, 0.128).</p>

	C.1.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Within the limitations of these data, there were no new safety signals identified in this patient population. 1 case of herpes meningitis was reported in the meta-analysis. No cases of PML were identified in the meta-analysis, however, PML has been reported in natalizumab treated paediatric patients in the post-marketing setting.
II/0098/G	This was an application for a group of variations. 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.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	02/02/2017	11/09/2017	SmPC	N/A
IAIN/0100	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	12/12/2016	n/a		
II/0097/G	This was an application for a group of variations. Update of section 4.4 of the SmPC to include information about the use of plasmapheresis (PLEX) or intravenous immunoglobulin (IVIg) which can affect meaningful interpretation of serum anti-JCV antibody testing, and update of sections 4.4 and 4.8 of the SmPC upon request by PRAC following the assessment of procedure SDA 063 regarding a signal on necrotising retinitis. The package leaflet has been updated accordingly. An updated RMP version 22.0	15/09/2016	11/09/2017	SmPC and PL	Use of plasmapheresis (PLEX) or intravenous immunoglobulin (IVIg) can affect meaningful interpretation of serum anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies within 2 weeks of PLEX due to removal of antibodies from the serum, or within 6 months of IVIg (i.e. 6 months = 5x half-life for immunoglobulins). Acute retinal necrosis (ARN) is a rare fulminant viral infection of the retina caused by the family of herpes viruses (e.g. varicella zoster). In post-marketing experience, rare cases of ARN have been observed in patients receiving TYSABRI. Some cases have occurred in patients with central nervous

	<p>was agreed during the procedure.</p> <p>C.I.3.a - 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 - Implementation of wording agreed by the competent authority</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>system (CNS) herpes infections (e.g. herpes meningitis and encephalitis). Serious cases of ARN, either affecting one or both eyes, led to blindness in some patients. The treatment reported in these cases included anti-viral therapy and in some cases, surgery. Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN. Following clinical diagnosis of ARN, discontinuation of TYSBABRI should be considered in these patients.</p>
N/0096	<p>Update of the package leaflet with revised contact details of the local representatives for Romania and Norway.</p> <p>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)</p>	30/06/2016	11/09/2017	PL	
II/0077	<p>Extension of Indication to include a new indication for Tysabri</p> <p>As a consequence, sections 4.1 and 4.4 of the SmPC were updated in order to provide physicians with more options for treating RRMS patients with high disease activity who fail a full and adequate course of treatment with disease modifying therapy (DMT). Consequential changes were also introduced in sections 4.2, 4.3, 5.1 of the SmPC.</p> <p>The Package Leaflet is updated in accordance.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p>	26/05/2016	24/06/2016	SmPC and PL	<p>Please refer to the scientific discussion of Tysabri H-000603-II-077-AR.</p>

II/0094/G	<p>This was an application for a group of variations.</p> <p>B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP</p> <p>B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>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</p> <p>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</p> <p>B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol</p> <p>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation</p> <p>B.II.f.1.e - Stability of FP - Change to an approved stability protocol</p>	23/06/2016	n/a		

A20/0083	<p>Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 29 April 2015 the opinion of the European Medicines Agency further new scientific evidence on progressive multifocal leukoencephalopathy (PML) in patients treated with Tysabri. The CHMP was requested to assess the impact thereof on the benefit-risk balance of Tysabri and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or revoked.</p> <p>As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.</p>	25/02/2016	25/04/2016	SmPC, Annex II and PL	Please refer to the assessment report: Tysabri EMEA/H/A-20/1416/C/000603/0083
II/0087	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/04/2016	n/a		
R/0091	Renewal of the marketing authorisation.	25/02/2016	18/04/2016	SmPC, Annex II, Labelling and PL	<p>Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Tysabri in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.</p> <p>In addition, sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) were updated to include new safety information on Granule Cell Neuronopathy (GCN), a condition which is also caused by John Cunningham Virus (JCV) and that has occurred in some patients who have been</p>

					given Tysabri. Symptoms of JCV GCN are similar to symptoms of Progressive Multifocal Leukoencephalopathy (i.e. cerebellar syndrome). The Package leaflet is being updated accordingly.
PSUSA/2127/201508	Periodic Safety Update EU Single assessment - natalizumab	17/03/2016	n/a		PRAC Recommendation - maintenance
II/0090	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	18/04/2016	SmPC	
II/0089	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	18/04/2016	SmPC, Annex II and PL	
II/0088	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	18/04/2016	SmPC and PL	
IG/0615	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	11/09/2015	n/a		
IB/0085	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	06/08/2015	n/a		
IAIN/0084/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	17/06/2015	18/04/2016	Annex II and PL	

	<p>or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient</p> <p>A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release</p>				
IB/0079	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	22/05/2015	n/a		
II/0074	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/05/2015	18/04/2016	SmPC	
IG/0558/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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)</p>	12/05/2015	n/a		

IA/0081/G	<p>This was an application for a group of variations.</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p>	08/05/2015	n/a		
IA/0080	<p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p>	30/04/2015	n/a		
IB/0078	<p>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</p>	30/04/2015	n/a		

II/0076/G	<p>This was an application for a group of variations.</p> <p>B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol</p> <p>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p>	23/04/2015	n/a		
PSUSA/2127/201408	Periodic Safety Update EU Single assessment - natalizumab	12/03/2015	n/a		PRAC Recommendation - maintenance
II/0072	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2014	n/a		
N/0073	<p>Update of the package leaflet with revised contact details of local representative for Estonia, Latvia and Lithuania.</p> <p>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)</p>	24/10/2014	13/11/2014	PL	

IB/0067	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/06/2014	n/a		
IA/0071	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	14/05/2014	n/a		
IA/0070	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	14/05/2014	n/a		
IA/0068	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	14/05/2014	n/a		
IG/0431	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	16/04/2014	n/a		
IB/0065/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.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the	15/04/2014	n/a		

	dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
PSUV/0064	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
IAIN/0063	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	26/11/2013	13/11/2014	SmPC and PL	
PSUV/0062	Periodic Safety Update	27/06/2013	26/08/2013		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation for PSUV/0062.
II/0059/G	This was an application for a group of variations. Extension of indication in RRMS population with high disease activity with the introduction of glatiramer acetate as an additional example of treatment failure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	30/05/2013	09/07/2013	SmPC and PL	Please refer to the scientific discussion Tysabri H-603-II-59-G AR
II/0060	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	27/06/2013		Annex II	

T/0061	Transfer of Marketing Authorisation	03/05/2013	13/06/2013	SmPC, Labelling and PL	Transfer of the Marketing Authorisation to Biogen Idec Limited.
II/0058	<p>Update of section 4.4 of the SmPC to recommend that patients and healthcare professionals should continue to be alert for any new signs and symptoms that may be suggestive of Progressive Multifocal Leukoencephalopathy (PML) for approximately 6 months following discontinuation of Tysabri since PML has been reported following discontinuation of Tysabri in patients who did not have findings suggestive of PML at the time of discontinuation. Annex II was also updated in accordance with the latest template.</p> <p>C.1.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	17/01/2013	13/06/2013	SmPC and Annex II	<p>Based on the review of the submitted data in patients who had onset of suspicion of PML after Tysabri discontinuation, the CHMP considered that the Marketing Authorisation Holder (MAH) assumption that PML occurs as Tysabri continues to have some pharmacological effect is one possible explanation and therefore accepted to include the following information in the SmPC:</p> <p>- Section 4.4: PML has been reported following discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation. Patients and Physicians should continue to be alert for any new signs or symptoms that may be suggestive of PML for approximately six months following discontinuation of TYSABRI.</p>
II/0057	<p>Update of section 4.4 of the SmPC to include a recommendation on testing frequency for anti-JCV antibody negative patients every 6 months based on review of post-marketing PML cases and clinical trial data in relation to the frequency of re-testing of anti-JCV antibody status in anti-JCV antibody negative patients.</p> <p>C.1.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	18/10/2012	19/11/2012	SmPC	<p>Based on the review of the submitted data, the CHMP considered that a six-monthly anti-JCV antibody testing would allow for an earlier identification of patients who have changed their antibody status from negative to positive. In addition, data on seroconversion, seroreversion and intermittent positivity over 30 months suggested a significant intrinsic variance of anti-JCV antibody status over time supporting the increased monitoring from every 12 months to 6 months. Considering that the recommended frequency of anti-JCV antibody testing was part of the Risk management plan only, the CHMP accepted to include a SmPC recommendation as well to further strengthen this monitoring. The following updated information on anti-JCV</p>

					<p>antibody testing appears in the SmPC:</p> <ul style="list-style-type: none"> - Section 4.4: Anti-JCV antibody testing provides supportive information for risk stratification of TYSABRI treatment. Testing for serum anti-JCV antibody prior to initiating TYSABRI therapy or in patients receiving TYSABRI with an unknown antibody status is recommended. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. The anti-JCV antibody assay (ELISA) should not be used to diagnose PML. Anti-JCV antibody testing should not be performed during, or for at least two weeks following, plasma exchange due to the removal of antibodies from the serum.
II/0056	<p>Changes to section 4.8 of the SmPC in order to update the safety information concerning the occurrence of elevated levels of eosinophils (eosinophil count >1,500/mm³) without clinical implications in patients taking Tysabri.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	18/10/2012	19/11/2012	SmPC and PL	<p>Based on 11 reported cases of hyper-eosinophilia (eosinophil count >1.5 x 10⁹/L), section 4.8 of the SmPC was updated in order to inform the healthcare professionals of the occurrence of this adverse reaction. No clinical symptoms associated with the hyper-eosinophilia were reported. However, stopping treatment resolved the situation.</p>
II/0055/G	<p>This was an application for a group of variations.</p> <p>Changes to simplify the clarification operations</p> <p>Addition of new test sites for the testing of unprocessed bulk harvest</p> <p>Widening of in process limits</p> <p>Change to reduce/remove a manufacturing facility environmental control</p> <p>Change to update the protocol used for the</p>	18/10/2012	18/10/2012		<ol style="list-style-type: none"> 1. Change to drug substance manufacturing process - replacement of clarification by microfiltration with clarification by centrifugation 2. Addition of new test sites for the testing of unprocessed bulk harvest. The test laboratories (Bioreliance) are located in US and EU. 3. Widening of In-Process Limits 4. Reduction/removal of a manufacturing facility environmental control. As natalizumab DS is dispensed into a

<p>qualification of new reference standards</p> <p>Change in reporting drug substance release in process microbial limits</p> <p>Change in reporting drug product release in process microbial limits</p> <p>Addition of new site for QA/QC testing (visual inspection)</p> <p>B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product</p> <p>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</p> <p>B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS</p> <p>B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test</p> <p>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</p> <p>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new</p>				<p>closed system (bag) it will no longer be transferred in the class 100 laminar flow hood. Activities will occur in the adjacent class 10,000 and 100,000 rooms. In addition, rooms used for product transfer/dispensing into storage container are being renamed.</p> <p>5. Update the protocol used for the qualification of new reference standards.</p> <p>6. A change is being implemented in the reporting of drug substance release in- process microbial limits. Test results will be reported in compliance with compendia for TYMC and TAMC.</p> <p>7. A change is being implemented in the reporting of drug product in process microbial limits. Test results will be reported in compliance with compendia for TYMC and TAMC</p> <p>8. Addition of Vetter Helmut as site for limited testing (visual inspection) of drug product</p>
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	<p>specification parameter to the specification with its corresponding test method</p> <p>B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product</p> <p>- Tightening of in-process limits</p> <p>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</p>				
II/0054	<p>Update of section 4.4 of the Summary of Product Characteristics (SmPC) to include further information on the clinical utility and testing of the anti-JCV antibody status to stratify the risk of developing PML prior or during treatment with Tysabri and to add a reference to the physician information and management guidelines for the quantification of PML risk in the different patient groups. Furthermore, the PML incidence estimate was deleted and the text related to treatment continuation in patients with the 3 identified risk factors for PML was updated. The Product information (including section 4.7 of SmPC) was also updated following assessment of the results of a User Testing Consultation (FUM 53).</p> <p>Implementation of the latest QRD template (version 8, July 2011) and editorial changes, including an update of the local representative details in Slovakia were also made.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	19/04/2012	25/05/2012	SmPC, Annex II, Labelling and PL	Based on continuing evaluation of the progressive multifocal leukoencephalopathy (PML) incidence rates the risk stratification algorithm has been updated based on postmarketing data, resulting in changes to the PML incidence figures for patients with antibodies against JCV or more additional risk factors. The CHMP considered that these revised PML incidence rates are not significantly different from the numbers that were included in the previous version and has concluded that the current benefit/risk assessment for the use of Tysabri in the indicated population remains unaltered. However, given that these numbers have changed, and will most likely continue to vary, the CHMP agreed to amend the statement in the SmPC by removing specific reference to the PML incidence estimates in order to replace it with a qualitative statement on the level of PML risk in the high risk subgroup, particularly since updated estimates will continue to be presented in the Physician Information and Management Guidelines and the treatment forms. The text on treatment continuation in patients with all three risk factors was updated to clarify that TYSABRI should only be continued if the benefits outweigh the risks.

					For JCV antibodies, the CHMP also agreed to reflect that this test should not be used for PML diagnosis in the absence of supportive data. In addition, on the basis of the review of further data, the CHMP agreed that anti-JCV antibodies samples must not be drawn during or for at least two weeks following the plasma exchange treatment (PLEX), since this may reduce the risk of collecting inaccurate data and hence accepted that this information is added into the SmPC.
II/0048	<p>the MAH has applied for a change to an in-process limit.</p> <p>B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS</p>	16/02/2012	16/02/2012		
IAIN/0053	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	01/02/2012	n/a		
II/0044	<p>To use an alternate pre-siliconised syringe stopper at the drug product manufacturing site Hospira Inc., i.e. in addition to an identical stopper which is siliconised and washed by the same method at the drug product manufacturing site.</p> <p>B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products</p>	19/01/2012	19/01/2012		

IB/0047/G	<p>This was an application for a group of variations.</p> <p>B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation</p> <p>B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation</p> <p>B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation</p>	13/01/2012	n/a		
IB/0045/G	<p>This was an application for a group of variations.</p> <p>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits</p> <p>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits</p>	13/01/2012	n/a		
IB/0050	<p>B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)</p>	03/01/2012	n/a		
IAIN/0052	<p>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</p>	22/12/2011	n/a		

IA/0051/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	22/12/2011	n/a		
IB/0049	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	19/12/2011	n/a		
IB/0046	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	19/12/2011	n/a		
N/0042	The Marketing Authorisation Holder (MAH) took the opportunity to update details of local representatives in Annex IIIB. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/11/2011	25/05/2012	PL	The Marketing Authorisation Holder (MAH) took the opportunity to update details of local representatives in Annex IIIB.
IA/0043	A.1 - Administrative change - Change in the name and/or address of the MAH	28/10/2011	25/05/2012	SmPC, Labelling and PL	
R/0040	Renewal of the marketing authorisation.	14/04/2011	17/06/2011	SmPC, Annex II, Labelling and PL	The benefit-risk balance remains positive for the MS population with less than 24 months exposure to Tysabri, even in the presence of prior immunosuppressive treatment and seroprevalence of JCV. In MS patients with longer than 24 months of exposure to Tysabri, the benefit-risk-balance is

					<p>favourable, albeit with a thinner margin of a positive effect over the recognised increased risk for developing PML</p> <p>The currently available information from post-marketing experience does not provide complete evidence of how the risk factors could combine and interfere on the benefit-risk balance in long-term exposed patients.</p> <p>Therefore, the CHMP is of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required.</p>
II/0041	<p>Update of section 4.4 of the SmPC to describe the 3 risk factors for PML that have been identified and to provide information on the level of risk of developing PML in Tysabri-treated patients depending on those 3 factors. This section is also updated to provide information on the clinical utility of testing the anti-JCV antibody to stratify the risk of developing PML prior or during the treatment with Tysabri. Section 4.2 is also amended to inform that after 2 years of treatment, patients should be re-informed about the risk factors for PML.</p> <p>The PL is amended accordingly.</p> <p>C.1.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	14/04/2011	16/06/2011	SmPC, Annex II and PL	<p>PML is associated with an uncontrolled increase of the JC virus in the brain, although the reason for this increase in some patients treated with TYSABRI is unknown. JC virus is a common virus which infects many people but does not normally cause noticeable illness.</p> <p>The risk of PML with TYSABRI is higher:</p> <p>" The longer that you are on treatment especially if you have been on treatment for more than two years. It is not known if the chance of getting PML continues to rise, remains the same, or falls after you have been on TYSABRI for more than three years.</p> <p>" If you have previously taken a medicine called an immunosuppressant. These medicines reduce the activity of your body's immune system.</p> <p>" If you have antibodies to the JC virus in your blood. These antibodies are a sign that you have been infected by JC virus.</p> <p>Patients who have all three risk factors for PML (i.e., have received more than 2 years of TYSABRI therapy, and have received prior immunosuppressant therapy and are anti-JCV antibody positive) have the highest risk of PML at</p>

					<p>approximately 9 in 1,000 patients treated.</p> <p>Testing for serum anti-JCV antibody prior to initiating TYSABRI therapy or in patients who are already being treated with TYSABRI but who have not previously been tested may provide additional information on the level of risk for PML.</p>
II/0038	<p>Update of section 4.5 of the SmPC to add information on the effect of Tysabri therapy on vaccination response.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	17/03/2011	20/04/2011	SmPC	<p>The MAH submitted results of a clinical trial evaluating the effects of Tysabri treatment on vaccination response in subjects with relapsing forms of multiple sclerosis. It was agreed that the information available is of relevance to prescribers. The following text was added to section 4.5 of the SmPC:</p> <p>Immunisations</p> <p>In a randomised, open label study of 60 patients with relapsing MS there was no significant difference in the humoral immune response to a recall antigen (tetanus toxoid) and only slightly slower and reduced humoral immune response to a neoantigen (keyhole limpet haemocyanin) was observed in patients who were treated with TYSABRI for 6 months compared to an untreated control group. Live vaccines have not been studied.</p>
II/0037	<p>Update of section 4.6 Fertility, Pregnancy and Lactation of the Summary of Product Characteristics (SmPC) to include in the breastfeeding section that Tysabri is excreted in human milk. Section 5.3 Preclinical Safety Data of the SmPC has been revised accordingly.</p> <p>In addition, the Annex II has been revised to reflect the latest approved version of the RMP and to introduce minor editorial changes.</p>	20/01/2011	21/02/2011	SmPC and Annex II	<p>At the time of the approval of Tysabri in the EU, there were no data available regarding the presence of Tysabri in the milk of female patients who were breastfeeding.</p> <p>Information regarding the ability of Tysabri to be found in human milk has been obtained.</p> <p>The SmPC has been amended to reflect the above, to read "TYSABRI is excreted in human milk. The effect of natalizumab on newborn/infants is unknown. Breastfeeding</p>

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				should be discontinued during treatment with TYSABRI."
IA/0039	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	06/01/2011	n/a		
II/0031	<p>Update of section 4.4 of the Summary of Product Characteristics (SmPC) to update safety information regarding the risk of PML in patients who have been treated with immunosuppressant therapy prior to receiving Tysabri.</p> <p>Section 2 of the Package Leaflet is revised accordingly. Additionally, the Product Information is updated in accordance with the latest QRD template.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	21/10/2010	29/11/2010	SmPC, Annex II and PL	<p>The MAH has analysed the data of 52 Tysabri treated patients with confirmed PML in respect of an association with prior immunosuppressant use (IS). The presented data indicate that prior IS use increases the risk of PML independent of the duration of Tysabri therapy.</p> <p>Sections 4.2 and 4.4 of the SmPC have been updated to reflect the above and the following text has been added to section 2 of the package leaflet:</p> <p>"The risk of PML is also greater if you have previously taken a medicine that weakens your immune system."</p> <p>In addition, it was agreed that the following warning statement would be added in the treatment initiation and treatment continuation forms: "The risk of PML is also greater if you have previously taken a medicine called an immunosuppressant that reduces the activity of your body's immune system".</p> <p>Finally, the Product Information has been updated in accordance with the latest QRD template (version 7.3.1 dated March 2010).</p>
IB/0032/G	<p>This was an application for a group of variations.</p> <p>B.I.b.2.e - Change in test procedure for AS or starting</p>	09/11/2010	n/a		

	<p>material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p> <p>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</p>				
IA/0035	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	23/09/2010	n/a	Annex II	
IB/0034	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/09/2010	n/a		
IA/0033/G	<p>This was an application for a group of variations.</p> <p>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)</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State</p> <p>B.II.c.2.a - Change in test procedure for an excipient -</p>	21/09/2010	n/a	Annex II and PL	

	Minor changes to an approved test procedure				
A20/0029	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 26 October 2009, the opinion of Committee for Medicinal Products for Human Use (CHMP) on measures necessary to ensure the safe use of Tysabri in view of the increased number of PML cases in patients treated with the above mentioned product and to review its impact on the risk-benefit balance.	20/01/2010	10/05/2010	SmPC, Annex II and PL	Please refer to the assessment report: Tysabri-H-C-603-A20-29.
IA/0030	To delete a site responsible for the manufacture of the active substance. IA_09_Deletion of manufacturing site	10/12/2009	n/a		
II/0028	Change in the in-process-controls during manufacture of the active substance. Change(s) to the test method(s) and/or specifications for the active substance	24/09/2009	30/09/2009		
II/0027	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Annex II of the product information has been updated to reflect the new version of the DDPS and to add the wording regarding the risk management plan in line with QRD requirements. Update of DDPS (Pharmacovigilance)	23/04/2009	26/05/2009	Annex II	The new version of the DDPS has been added to module 1.8. The MAH also provided all necessary documentation to support the change in Qualified Person for Pharmacovigilance.

II/0026	<p>Update of the section 4.8 of the Summary of Product Characteristics and section 4 of the Package Leaflet to include updated information relating to symptoms that associated with hypersensitivity reactions reported as part of post-marketing surveillance.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>	18/12/2008	23/01/2009	SmPC and PL	<p>The MAH reviewed in the 3rd PSUR symptoms often reported concomitantly with possible hypersensitivity reactions with Tysabri. The most common symptoms included chest pain, dyspnoea, blood pressure increases or decreases, skin and cutaneous disorders (mostly of an urticarial nature). Angioedema was also rarely reported. The MAH included the following text to the hypersensitivity section in section 4.8 of the Summary of Product Characteristics: "In post-marketing experience, there have been reports of hypersensitivity reactions which have occurred with one or more of the following associated symptoms: hypotension, hypertension, chest pain, chest discomfort, dyspnoea, angioedema, in addition to more usual symptoms such as rash and urticaria."</p>
II/0024	<p>Change in the Active Substance manufacturing process. Consequential change in the Drug Product specifications.</p> <p>Change(s) to the manufacturing process for the active substance</p>	20/11/2008	19/12/2008	Annex II	
II/0025	<p>Update of sections 4.4, 4.8 and 5.2 of the SPC, sections 2 and 4 of the PL, RMP and patient alert card in order to include additional information on Progressive Multifocal Leukoencephalopathy (PML) and plasma exchange.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>	25/09/2008	30/10/2008	SmPC and PL	<p>Approximately 38,700 patients have been treated worldwide with Tysabri (natalizumab) since it has been approved, and 4,650 patients received Tysabri during clinical trials. Two cases of a rare brain infection called progressive multifocal leukoencephalopathy (PML) have been confirmed since the product is on the market phase in multiple sclerosis patients treated with Tysabri. Two PML cases were previously reported during clinical trials in patients treated with Tysabri in combination with interferon beta, leading to special warnings in the product information and extensive risk</p>

					<p>minimisation measures, including physician information and management Guidelines.</p> <p>In the two new above mentioned cases reported from the market, Tysabri was given as monotherapy, and for approximately 17 and 14 months. Both patients have undergone plasma exchange to reduce natalizumab levels. The marketing authorisation holder has performed a study investigating the effect of plasma exchange on Tysabri levels which showed that this leads to reduction of natalizumab levels faster than simply discontinuing Tysabri. However, the impact of plasma exchange on the restitution of immune function and ultimately its clinical usefulness is unknown.</p> <p>Patients treated with Tysabri must be regularly monitored for any clinical signs suggestive of PML. If PML is suspected, treatment must be suspended and further evaluations carried out as described in the physician information and management guidelines. Administration of Tysabri may resume only once the clinician has excluded PML, if necessary by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains. The benefit/risk profile of Tysabri remains positive in the authorised indication.</p>
II/0023	<p>Change in filtration cartridges used in the active substance manufacture.</p> <p>Change(s) to the manufacturing process for the active substance</p>	25/09/2008	02/10/2008		
II/0022	Inclusion of an alternative active substance container	25/09/2008	02/10/2008		

	closure system. Change(s) to the manufacturing process for the active substance				
II/0020	Extension of the shelf-life of the finished product from 2 to 4 years. Change(s) to shelf-life or storage conditions	24/07/2008	03/09/2008	SmPC	
II/0019	Change to the release and stability specification for the active substance and the finished product which do not impact on the benefit-risk balance. Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	24/07/2008	28/07/2008		
II/0021	Update of Summary of Product Characteristics and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	20/06/2008	SmPC and PL	A number of serious suspected hepatic reactions, including increased liver enzymes and hyperbilirubinaemia, were reported in patients receiving Tysabri since the medicine was put on the market in November 2004. All cases but one were reported from post marketing surveillance and occurred as early as six days after the first dose of Tysabri. All cases had at least one confounding risk factor but two cases were assessed as likely to be related to Tysabri. In these two cases, liver problems improved when Tysabri was stopped, but reappeared after readministration.
II/0017	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) and section 3 the	19/03/2008	25/04/2008	SmPC, Annex II, Labelling	The MAH reviewed the data (spontaneous reports and clinical trials) made available during the post-marketing phase on

	<p>Package Leaflet to include information on hypersensitivity reactions and herpes infections.</p> <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p>			and PL	<p>allergic reactions occurring in patients treated with Tysabri. Based on this review, it is concluded that the risk for allergy is greatest with early infusions and in patients re-exposed to TYSABRI following an initial short exposure (one or two infusions) and extended period (three months or more) without treatment. Since patients who have received an initial short exposure to TYSABRI and then had an extended period without treatment are more at risk for allergy upon re-dosing, continuous dosing with TYSABRI is important, especially during the first few months of treatment. The MAH also reviewed the data (spontaneous reports and clinical trials) made available during the post-marketing phase on herpes infections. Based on this review, it is concluded that in clinical trials, herpes infections (Varicella-Zoster virus, Herpes simplex virus) occurred slightly more frequently in patients treated with Tysabri than in patients receiving placebo.</p>
II/0018	<p>Change(s) to the test method(s) and/or specifications for the active substance</p> <p>Change(s) to the test method(s) and/or specifications for the finished product</p>	19/03/2008	31/03/2008		
II/0016	<p>Addition of an alternate contract site for the manufacture of the finished product and consequential changes.</p> <p>Change(s) to the manufacturing process for the finished product</p>	21/02/2008	26/02/2008		
II/0013	<p>Change(s) to the manufacturing process for the finished product</p>	18/10/2007	24/10/2007		

N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/09/2007	n/a	PL	
IA/0014	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	30/07/2007	n/a		
IA/0012	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	09/07/2007	n/a		
IA/0011	IA_09_Deletion of manufacturing site IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	06/06/2007	n/a		
II/0007	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	22/03/2007	28/03/2007		
II/0006	Change(s) to the manufacturing process for the active substance	22/02/2007	27/02/2007		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/12/2006	n/a	PL	
II/0003	Change(s) to the manufacturing process for the active substance	16/11/2006	27/11/2006		
II/0001	Change(s) to the manufacturing process for the finished product	16/11/2006	27/11/2006		

II/0002	<p>This variation relates to the introduction of administrative changes to the SPC, Labelling and Package Leaflet and the implementation of QRD template version 7.1. In addition, the marketing authorisation holder (MAH) proposed amendments to the presentation of AFFIRM trial data in section 5.1 of the SPC.</p> <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p>	18/10/2006	18/11/2006	SmPC, Labelling and PL	<p>The main change in this variation relates to the deletion of the mean values of time to progression in the AFFIRM study in section 5.1 of the SPC (Pharmacodynamic properties). Due to the large numbers of events censored in this analysis, these values represent an underestimate of the true values. The hazard ratio is considered a better way to represent the risk of progression and is theoretically stable over time whereas values for time to progression can range widely depending on which percentile is selected. When the event rates are low and the 1st quartile is not even reached, the outcome is best evaluated through the hazard ratio.</p>
IA/0004	<p>IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site</p> <p>IA_08_b_01_Change in BR/QC testing - repl./add. manif. responsible for BR - not incl. BC/testing</p>	12/10/2006	n/a	SmPC and PL	