



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Assessment report for TYSABRI

International Non-proprietary Name: natalizumab

Procedure No. EMA/H/C/000603/A20/0029

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.



1. Executive summary

Tysabri (Natalizumab) was granted a Marketing Authorisation on 27 June 2006 for use as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) in patients with high disease activity despite treatment with a beta-interferon or in patients with rapidly evolving severe relapsing remitting multiple sclerosis.

With increasing post-marketing experience and duration of exposure to natalizumab, the continued reporting of MS patients diagnosed with PML has raised concerns, especially because these data suggest, that risk for developing PML increases significantly after two years of continuous exposure.

On 22 October 2009, the CHMP requested a Review of the benefits and risks for Tysabri in view of new cases of progressive multifocal leukoencephalopathy (PML) that have been observed since Tysabri has been on the market and in consideration of the occurrence of IRIS in these patients once Tysabri has been stopped and PLEX and/or immunoabsorption has been implemented.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 26 October 2009 to assess the above concerns and its impact on the benefit/risk for Tysabri, and to give its opinion on measures necessary to ensure the safe use of Tysabri, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

2. Scientific Discussion

Tysabri (natalizumab) was granted a Marketing Authorisation on 27 June 2006 for use as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) in patients with high disease activity despite treatment with a beta-interferon or in patients with rapidly evolving severe RRMS.

Progressive multifocal leukoencephalopathy (PML) is a known rare adverse drug reaction occurring under Tysabri therapy. PML is brain infection caused by JC Virus (JCV), type of human polyomavirus. This virus is commonly found in the general population but only leads to PML if the immune system has been weakened. Like multiple sclerosis (MS), PML causes damage to the protective sheath surrounding nerves and it usually leads to severe disability or death. The symptoms of PML are very similar to those of an MS attack.

Twenty-three confirmed cases of PML had been reported worldwide in patients with Multiple sclerosis (MS) receiving Tysabri between July 2008 and October 2009, resulting in four deaths. With increasing post-marketing experience and duration of exposure to natalizumab, the continued reporting of MS patients diagnosed with PML raised concerns, especially because these data suggest, that risk for developing PML increases significantly after two years of continuous exposure. In October 2009 the CHMP together with the European Commission initiated an Article 20 review of the benefits and risks for Tysabri in view of the cases of PML that have been observed since Tysabri has been on the market and in consideration of the occurrence of Immune Reconstitution Inflammatory Syndrome (IRIS) in these patients once Tysabri has been stopped and Plasma Exchange (PLEX) and/or immunoabsorption (IA) was implemented.

By the end of the review procedure on 20 January 2010, the total number of confirmed PML cases had risen to 31 worldwide, of whom 23 had been receiving Tysabri for more than two years. This is equivalent to around one case of PML for every 1,000 patients treated with Tysabri for two years or more.

2.1. Clinical aspects

2.1.1. Progressive Multifocal Leukoencephalopathy (PML) - Risk over time

The CHMP reviewed Tysabri after it had received reports of side effects in patients receiving the medicine. As mentioned above, these included 23 confirmed cases of PML reported worldwide between July 2008 and October 2009, resulting in four deaths. Fourteen of these cases, including one death, were reported in the EU. By the end of the review procedure on 20 January 2010, the total number of

confirmed PML cases had risen to 31 worldwide, of whom 23 had been receiving Tysabri for more than two years. This is equivalent to around one case of PML for every 1,000 patients treated with Tysabri for two years or more.

It has been seen that PML case frequency increases over time. At present it is observed that the frequency of PML cases increase dramatically after 24 months (monthly infusions) of treatment. Although the scientific community is unanimous on that aspect and that it is not yet scientifically possible to prevent the appearance of this adverse event, efforts are being made for the early diagnosis of the cases.

The CHMP consulted the SAG-CNS on this respect. Following the discussions regarding the diagnosis of PML and the responses of the MAH, the SAG-CNS advised that a number of initial steps should be taken for treated patients. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML (such as impaired cognition, visual disturbances, hemiparesis, altered mental state or behavioural changes).

If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are possibly suggestive of PML. If any doubt exists, further evaluation, including Magnetic Resonance Imaging (MRI) scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC viral DNA and repeat neurological assessment, should be considered.

MRI is still the mainstay for early diagnosis of PML and thus important for the clinical outcome of the patients. In some circumstances, especially when lesions may occur in non eloquent regions of the brain, MRI may be more useful than clinical presentation for diagnosis of PML.

It is considered that an initial full MRI should be performed and be used as a baseline reference point. This full MRI should be performed within 3 months before the start of treatment with Tysabri, and then it should be repeated yearly thereafter, in order to have always a recent baseline reference.

The necessity for a diagnostic MRI should be driven by the clinical assessment of the patient at the monthly infusion visit. This diagnostic MRI may be required within a 1 or 2 weeks after the clinical assessment if there is an evolving neurological disorder. Patients and their relatives/carers should be supplied with suitable information to allow them to recognise any worrying symptoms that might signal a neurological event.

Concerning the sequences to be employed in the MRI (both reference and diagnostic), a full MRI it is favoured with a qualified neuroradiologist/radiologist interpreting the scan.

PLEX/IA has often been used to reduce the levels of Tysabri more quickly when PML has been identified. Plasma Exchange (PLEX) should be started if the diagnosis is confirmed either virologically or clinically with imaging data.

2.1.2. Immune Reconstitution Inflammatory Syndrome (IRIS)

PML appears to be followed by IRIS (Immune Reconstitution Inflammatory Syndrome) in almost all patients, and data suggest considerable worsening of the neurological condition of the patients. The use of PLEX/IA seems to accelerate the development of IRIS, immune reconstitution inflammatory syndrome, in the following days to weeks. While this is a necessary step towards elimination of the virus and containment of PML, it can lead to clinical worsening (i.e. IRIS) if the inflammatory reaction is intense and extended enough. IRIS is probably an enhanced viral clearance by the immune system and can lead to a severe pathology. Monitoring for development of IRIS and appropriate treatment of the associated inflammation during recovery from PML should be undertaken.

The impact of IRIS on the clinical management recommendations for PML patients was discussed as well as the evidence to recommend steroid treatment in the patients with IRIS. The discussion also included the current evidence on the use or not of steroids for the treatment of IRIS. The recommendation is that treatment could be started with a high dose systemic steroid at the first signs of IRIS. The patients should be monitored closely as IRIS should be considered as potentially inevitable syndrome after PLEX. The patients should be treated in a centre with intensive care facilities (ICU) to ensure a better outcome.

2.1.3. JVC and CSF test by PCR

The discussion on the validity as confirmatory or not of a positive CSF PCR for JCV virus was discussed at the CHMP.

The conclusion is that a negative CSF PCR for JCV virus, due to a potentially low number of viral copies, does not automatically mean the exclusion of PML. If the MRI and clinical picture suggest PML, CSF PCR for JCV virus should be undertaken. If the PCR is negative a further scan at an interval of 1-2 weeks is warranted to study progression of the brain lesions. PML can be diagnosed on clinical and imaging grounds, even when CSF PCR fails to provide virological confirmation. If the diagnosis of PML remains doubtful, the next natalizumab infusion should be delayed until further notice. It is suggested that potentially a 3-month period exist before a significant increase in the chance of a MS relapse.

Ideally, however, a laboratory using a state-of-the art CSF-PCR system provided from a reference laboratory, should perform the CSF virological monitoring once suspicious MRI lesions are found. ELISA as an alternative way of testing for the virus is not recommended as it is much less sensitive than PCR; as the antibody titres are low, they might go undetected.

This issue has been explained in the DHPC which the MAH is issuing in relation to this Article 20 review procedure.

2.1.4. Definition of non-responders and evidence for the use of glatiramer acetate (GA)

During the scientific discussions at the SAG-CNS and at the CHMP although there is a wide agreement on the patients identified for treatment with Tysabri, the national practices may vary. For that reason it was initiated again the discussion on the definition of the patients for Tysabri treatment. As presented in the Product Information the patients to be treated with Tysabri should be in one of the following categories:

- *Patients with high disease activity despite treatment with a beta-interferon (see section 5.1);*
- *These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of a beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.*

or

- *Patients with rapidly evolving severe relapsing remitting multiple sclerosis (see section 5.1). defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.*

In some countries it is considered as a full course of previous treatment to be an one-year course of glatiramer acetate (GA) (instead of beta interferon), and do not consider that subsequent use of interferon is likely to be of benefit if the patient starts to deteriorate on GA. For that reason the MAH was requested to submit any data regarding the treatment of patients initially with GA prior to initiation of the treatment with Tysabri. The MAH has submitted summaries of studies as well as bibliographic data. However the CHMP considered that the evidence did not allow to reach a satisfactory conclusion and requested the MAH to submit a FUM with all data available. The MAH has accepted this by including the commitment in a Letter of Undertaking (LoU).

2.1.5. Future Studies

2.1.5.a Treatment Interruption Study

There was no support for a routinely interruption of the treatment (referred as well as “drug holiday”) to reduce the risk of PML. Also, there is no equally effective drug that could be administered during the treatment interruption, thus leaving patients vulnerable to MS relapse.

It is important that patients should be re-evaluated and re-informed if treatment is to be continued beyond 24 months. This re-evaluation should consider whether treatment is still required, and the doctor and patient/carer should discuss the different risk involved in continued treatment beyond 24 months.

Suspension of treatment may increase the risk of antibody formation and hypersensitivity reactions when treatment is reintroduced. The MAH during the oral explanation to the SAG CNS mentioned their intention to submit for evaluation further information concerning the incidence of antibody formation stratified by treatment duration.

The MAH has already in place a post-authorisation commitment looking into these additional studies and also re-affirmed its commitment in a LoU.

2.1.5.b Development of a serological test for JCV.

The MAH has indicated in their responses that an evaluation on whether prior exposure and infection with JCV, as evidenced by the presence of antibodies to JCV in the serum, may be an additional risk factor for the development of PML. Also implicit in this concept is the possibility that the absence of JCV antibodies in the serum may identify a sub-group of patients who may be at a lower risk of PML compared to patients who are JCV antibody positive. The MAH in their responses has analysed blood samples in the original 3 patients who developed PML as part of the natalizumab clinical trials, and all these 3 patients were seropositive for antibodies against the JC virus prior to starting Tysabri (and thus 2 to 3 years prior to the onset of PML). In addition, the MAH recently determined that in 5 of the patients who developed PML since the marketing of natalizumab, blood samples from time points prior to starting natalizumab (approximately 2 to 3 years prior to the onset of PML) were available for testing. The MAH determined that all 5 of these post-marketing PML patients were also seropositive for antibodies against the JCV. The MAH has also evaluated the prevalence of JCV antibody positivity in approximately 1000 MS patients enrolled in clinical trials and found it to be approximately 50%. Given this prevalence of seropositivity in MS patients, it seems unlikely due to chance alone that all 8 PML patients for whom samples were available had been seropositive for JCV antibodies prior to the onset of PML. The MAH is still in the process of refining the assay for JCV antibody testing and evaluating approaches by which to confirm these results (e.g. through broader serum sample collection in natalizumab-treated MS patients), and is in discussions with PML and neurology experts to evaluate the significance and potential implications of these findings.

The CHMP requested that the validation data of the test used by the MAH should be submitted. The CHMP also requested for a formal protocol of this investigation including milestones and timelines. The MAH has accepted this in a LoU.

The MAH has developed an ELISA to detect, confirm, and determine the titer of anti-JCV antibodies in serum or plasma. The preliminary data generated from MS patients treated with TYSABRI using this method indicates sero-prevalence rates of approximately 45%, which are similar to what is reported for healthy subjects, and raises the possibility that this assay may be a useful tool to identify JCV infection rates in MS patients and help in PML risk stratification. The sponsor is continuing investigations using this methodology with a view to ultimately delivering a tool that could stratify patients depending on risk of PML. To achieve this goal a biomarker sampling study is planned.

2.2. Pharmacovigilance

2.2.1. Risk minimisation activities

Changes to the SPC and the Package Leaflet

Changes in [section 4.2](#) of the SPC “Posology and Methods of administration” were made in order to inform the physician that apart from the patient alert card which should be given to the patient, the patient should additionally be informed about the risks of Tysabri. After 2 years of treatment, patients should be re-informed about the risks of Tysabri, especially the increased risk of PML, and should be instructed together with their caregivers on early signs and symptoms of PML.

Changes in [section 4.4](#) of the SPC “Warnings and precautions for use” to inform the physicians of the fact that the risk of PML appears to increase with treatment duration, especially beyond 2 years. Due to this increased risk of developing PML, the benefits and risks of Tysabri treatment should be individually reconsidered by the specialist physician and the patient. The patient should be re-informed about the risks of Tysabri after 2 years especially the increased risk of PML, and should be instructed together with their caregivers on early signs and symptoms of PML.

The section 4.1 “Therapeutic Indication” has been rearranged. The definition of the patients eligible to receive Tyasbri has been moved from section 5.1 of the SPC. No additional changes have been made at this stage; this issue will be re-discussed in a future variation.

The Package Leaflet has been amended to reflect the information about the increased risk on PML over time as well to include awareness on IRIS.

Controlled Treatment Environment – Registries or Observational studies

The Committee noted that there are no known ways to prevent or treat PML, so it is important that the symptoms of the disease are detected as soon as possible.

Therefore, it is generally acknowledged that a more controlled treatment environment is needed for patients prescribed with Tysabri.

Registries exist already in some countries (e.g. Italy, Sweden). Post-marketing studies for data collection have been going on for sometime in other countries (e.g. TYSDEMUS, France). Between them, the registries and observational studies account for over 50% of Tysabri patients in Europe.

Two EU-wide observational studies are sponsored by the MAH. The TYGRIS study has completed recruitment of over 4,000 patients in EU and observation is continuing. A new study, TOP has also been initiated. This is collecting the same safety data as TYGRIS but, in addition, is also collecting efficacy data.

In that respect, the entry of all patients into a registry and/or to an observational study was highly recommended during the CHMP discussions. However recognising that there are differences in National Legal frameworks, the CHMP recommends that the National Competent Authority in each Member State shall discuss and agree with the MAH the details of how patients will be continuously monitored in their territory and ensures that the MAH takes the appropriate measures to implement this. The MAH shall implement any agreed measures for monitoring within a time frame agreed with the National Competent Authority.

Treatment Initiation and Continuation Forms

It is essential that the patients are fully informed of the risks at the beginning of the treatment of Tysabri as well as later at around 24 months when the risk of PML increases. For that reason the MAH has agreed with the CHMP to facilitate the information flow to the patient via the treating physician with the provision of the treatment initiation and treatment continuation forms. These forms aim exclusively to highlighting the risk to the patients and making sure that this is transmitted to them via their physician.

The aim of the treatment initiation form is intended to protect patients by ensuring that they are fully informed of, and understand the risk of PML, IRIS and other important adverse effects of Tysabri. Confirmation that the doctor has discussed the risks of PML and the risk of IRIS if treatment is

discontinued following suspicion of PML will be included. Affirmation of patient understanding of the risks of PML and that they have received a copy of the form as well as a patient alert card will be in place.

The treatment continuation forms should contain the elements of the treatment initiation form and in addition a statement that the risks of PML increase with duration of treatment and that treatment beyond 24 months carries additional risk.

Patient Alert Card

A patient alert card was already in place for Tysabri. However during this Article 20 review discussion the card has been updated to provide more information on the symptoms of PML in order to alert the patients as well their care givers for an early detection of the symptoms. Also as the risk for PML increases over time, the date when the treatment started is recommended to be added.

During the consultation with the MS patients' organisations it was revealed that the format of this card may need to be further adapted to the needs of the MS patients.

The amended Patient Alert card was adopted by the CHMP.

2.3. Product Information

The CHMP recommended the amendments to be introduced in the Summary of Product Characteristics (SPC), Annex II, and Package Leaflet. In addition the CHMP has recommended changes to the Annex IV.

Summary of Product Characteristics

The Section 4.1 "Therapeutic Indication" has been rearranged. The definition of the patients eligible to receive Tyasbri has been moved from section 5.1 of the SPC.

The Section 4.2 "Posology and method of administration" has additional information that in addition to the Patient Alert card the patient needs to be informed about the risks of Tysabri. After 2 years of treatment, patients should be re-informed about the risks of Tysabri, especially the increased risk of PML, and should be instructed together with their caregivers on early signs and symptoms of PML.

The Section 4.4 "Special warnings and precaution for use" has additional information on PML and the information needed to be available to each individual patient in order to minimise the risk. In addition new information on development of IRIS in relation to PML has been added. Information on the monitoring for development of IRIS has been added.

Annex II – Conditions of Marketing Authorisation

The Annex II of the product information was extensively amended to include the new requirements on the Registries/Observational studies as well as on the Treatment Initiation and Continuation form as it was extensively presented previously in this report.

Package Leaflet

The package Leaflet has been updated to reflect the changes in the SPC, especially section 2 with information on PML. In this section the increased risk over time is also highlighted for the patient and caregiver. Information on the risk of developing IRIS is also included. In general the PL has been aligned to the SPC added information.

Annex IV – Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the MS

The Competent authority in each Member State shall discuss with the MAH the details of how patients will be monitored in their territory and ensure that, as appropriate, the MAH, or other body as agreed, takes the appropriate measures to implement the activities.

The Member States shall discuss and agree the physician pack with the MAH and ensure that the MAH provides all physicians who intend to prescribe TYSABRI with a physician pack containing the agreed elements. That includes the Product Information, Physician information about TYSABRI, Patient Alert cards as adopted by the CHMP, and Treatment initiation and treatment continuation forms.

3. Discussion and Benefit/risk assessment

The CHMP concluded that the benefit still outweighs the risks for the patients treated with Tysabri. The CHMP also concluded that the Product Information for Tysabri should include safety information aiming at informing patients and physicians about the risk of PML so that the symptoms are detected as soon as possible and therefore recommended the amendments to the relevant sections of the Summaries of Product Characteristics and Package Leaflet

In addition the Conditions of the Marketing Authorisation (Annex II) as well as the Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States (Annex IV) were also amended.

The CHMP also recommended that a dialogue is put continuously in place between the MAH and the Regulatory Authorities for further updates on the implementation of the risk minimisation measures as well on the scientific developments currently ongoing to further investigate PML.

Benefit/Risk Balance

Taken this into account, the benefit/risk balance for natalizumab is considered favourable.

4. Overall Conclusion

Having considered the overall data provided by the MAH in writing and in the oral explanation, the CHMP concluded that the benefit still outweighs the risks for the patients treated with Tysabri. The CHMP also concluded that the Product Information for Tysabri should include safety information aiming at informing patients and physicians about the risk of PML so that the symptoms are detected as soon as possible and therefore recommended the amendments to the relevant sections of the Summaries of Product Characteristics and Package Leaflet.

In addition the Conditions of the Marketing Authorisation (Annex II) as well as the Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States (Annex IV) were also amended.

The CHMP also recommended that a dialogue is put continuously in place between the MAH and the Regulatory Authorities for further updates on the implementation of the risk minimisation measures as well on the scientific developments currently ongoing to further investigate PML.

Therefore the CHMP recommended the variation of the Marketing Authorisation of Tysabri for which the Summary of Product Characteristics is set out in Annex I of the Opinion.

The CHMP agreed on the amendments to be introduced in the SPC, Annex II, Package Leaflet, and Annex IV.

The scientific conclusions and the grounds for the amendment of the SPC, Annex II, and Package Leaflet and Annex IV are set out in Annex V of the Opinion.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below (as per the MAH's Letter of Undertaking):

Area	Description	Due Date
Clinical	<p>1. Study description and protocol for a treatment interruption study.</p> <p>2. Study description for the development of a serological test for JCV.</p> <p>3. Submission of data in support of the use in patients of GA (glatiramer acetate) prior to the initiation of treatment with Tysabri.</p> <p>4. Submission of the results of the panel of experts consulted regarding IRIS on 11 June 2009.</p> <p>5. The MAH will update regularly the EMA and the CHMP on the cases of PML (confirmed and suspected) and will provide detailed discussions in future PSURs.</p> <p>6. The MAH will update in future PSURs the current investigations being undertaken for the development of biological markers capable to identify a population at risk for developing PML or dose investigation studies (PK and efficacy studies) that could provide an opportunity for risk minimisation.</p>	<p>14/02/2010</p> <p>14/02/2010</p> <p>4Q2010</p> <p>when available</p> <p>Monthly cumulative listings for information and detailed analysis for evaluation in future PSURs</p> <p>in future PSURs</p>
Pharmacovigilance	<p>7. The MAH shall provide a full update to the EU risk management plan for Tysabri to include full details of risk minimisation activities in addition to those already in place for Tysabri introduced as part of the Article 20 procedure. This full update will also contain study and test development protocols of the above studies 1, 2 and 4 and milestones.</p> <p>8. The MAH shall provide the European Medicines Agency with an update on the implementation of the risk minimisation activities and monitoring system in each Member State in future PSURs.</p>	<p>14/02/2010</p> <p>14/02/2010</p> <p>in future PSURs</p>

5. Action Plan

As part of this procedure, the MAH and the CHMP agreed the wording of a Dear Healthcare Professional Communication (DHPC) designed to inform prescribers of the Tysabri.

The Product Information will be immediately published in the European Medicine Agency's website together with a Press Release and Question and Answers document.

6. Conclusion and Grounds for the Recommendation

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Tysabri initiated by the European Commission.
- The Committee considered all the available data submitted by the MAH on the safety of Tysabri in relation to the increased risk of PML over time and the further development of IRIS.
- The Committee concluded that benefit still outweighs the risks for the patients treated with Tysabri.
- The CHMP concluded that the Product Information for Tysabri should include safety information aiming at minimising the risk of PML and therefore recommended the amendments to the relevant sections of the Summaries of Product Characteristics, and Package Leaflet. Furthermore, Risk Minimisation Measures aiming at increasing the awareness of the healthcare professionals as well as patients and their carers regarding the increased risk of PML over time and the measures set in place for the early diagnosis of the condition are recommended and updated accordingly.
- The CHMP recommended that Annex II Conditions of the Marketing Authorisation as well as Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states (Annex IV) were also amended.

The Committee, as a consequence, concluded that the benefit/risk balance of Tysabri is positive under normal conditions of use.